Retinal waves: experiments and theory

Bruno Cessac, Dora Karvouniari, Lionel Gil, Olivier Marre, Serge Picaud

Retinal waves: experiments and theory

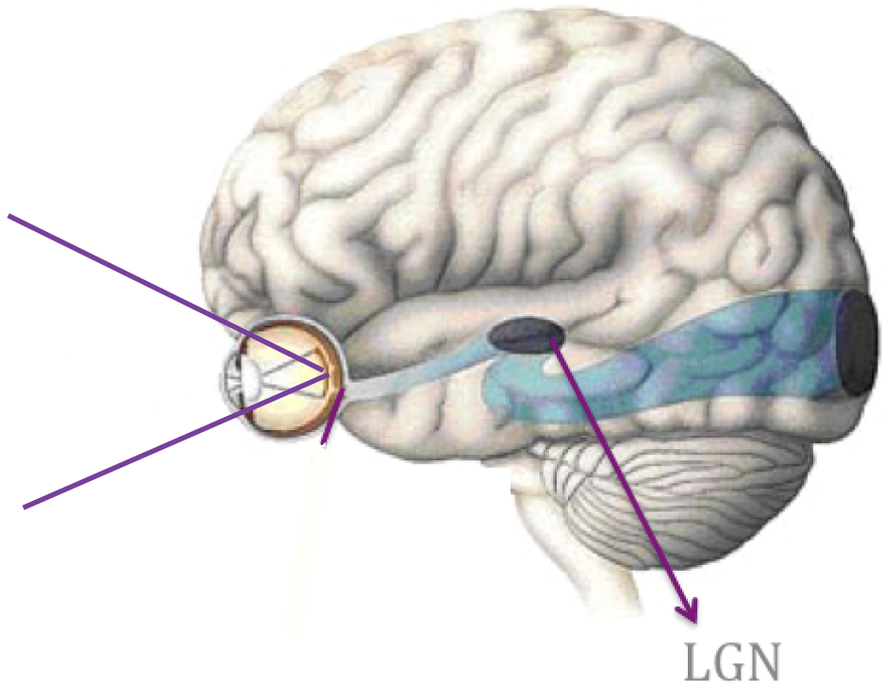
D. Karvouniari, Biovision team, INRIA, Sophia Antipolis

L. Gil, INLN, Sophia Antipolis
O. Marre, Institut de la Vision, Paris
S. Picaud, Institut de la Vision, Paris
B. Cessac, Biovision team, INRIA, Sophia Antipolis

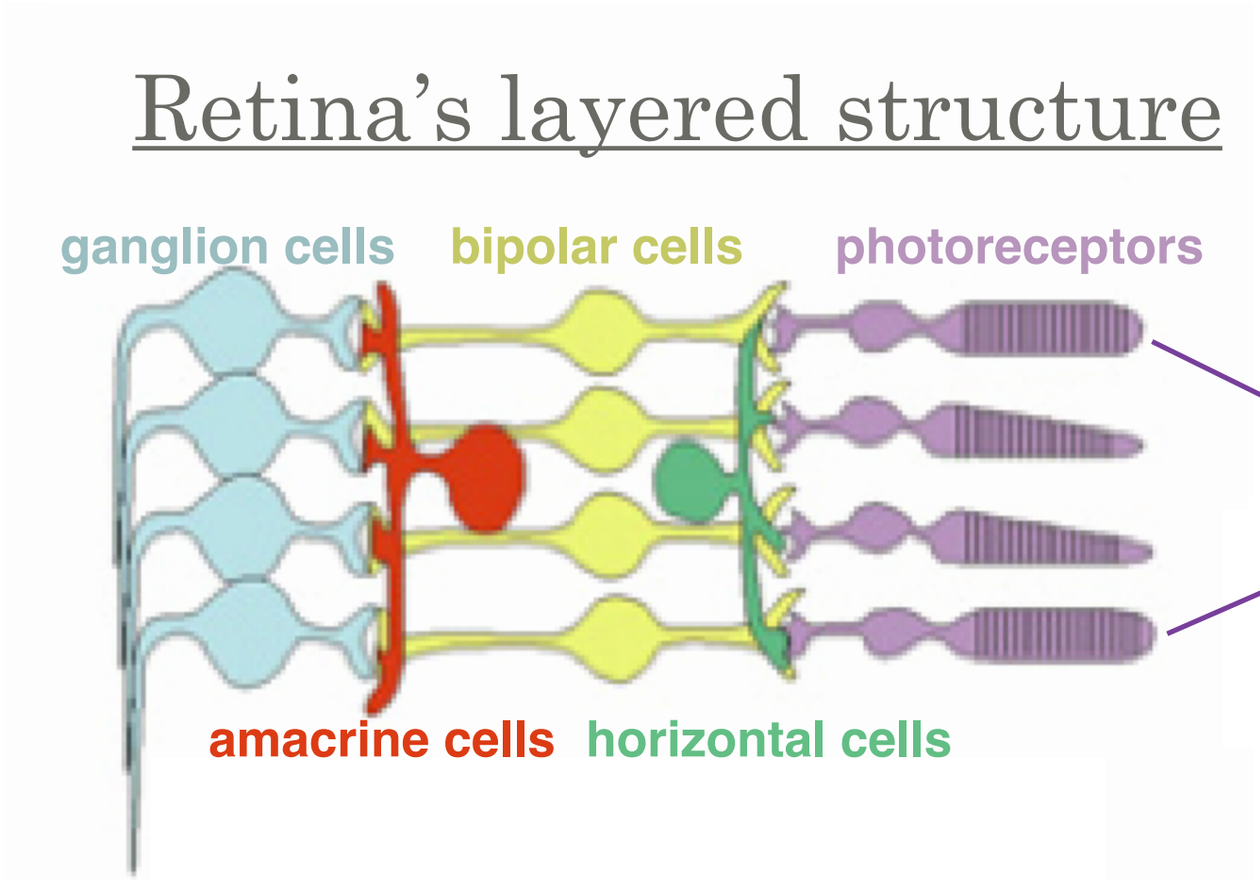
Acknowledgement: M. Hennig, E. Sernagor.

The structure of the <u>adult retina</u>

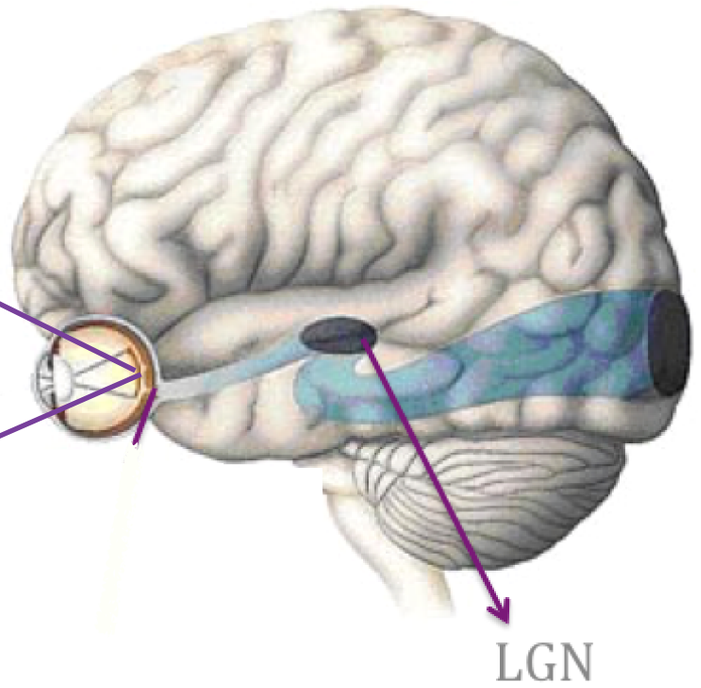
Light



The structure of the adult retina

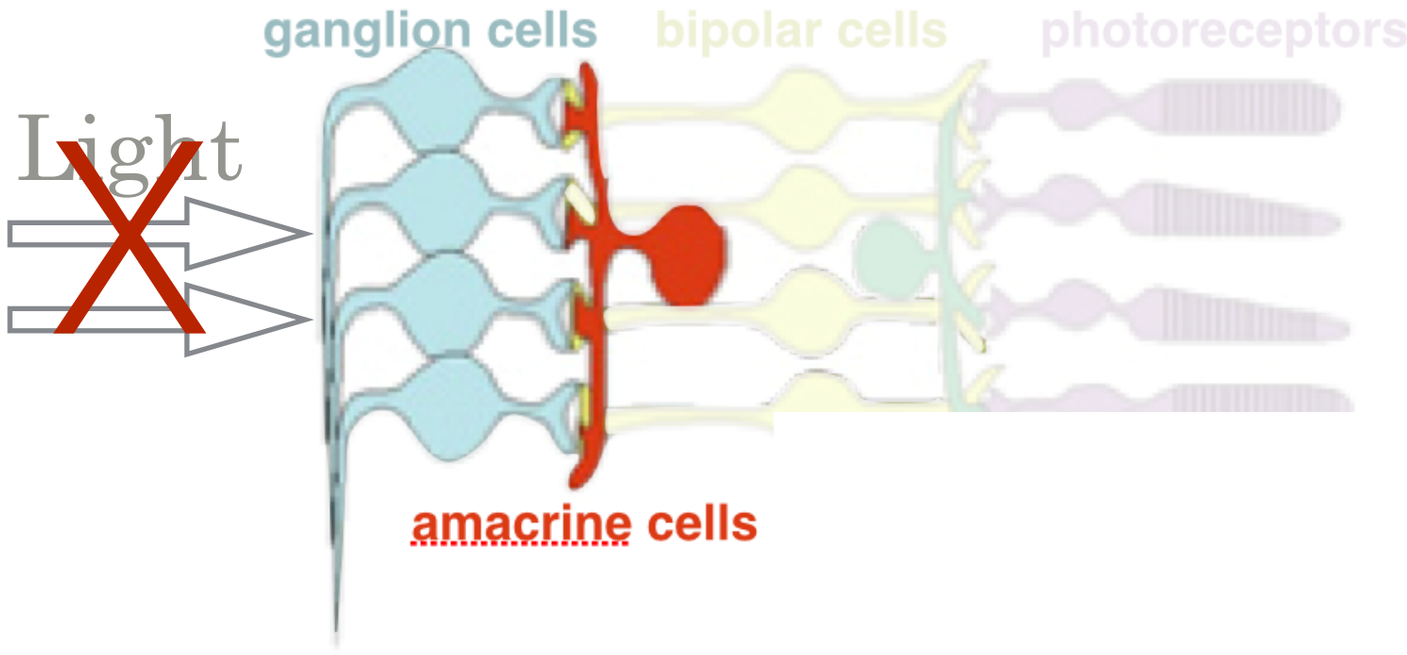


Light



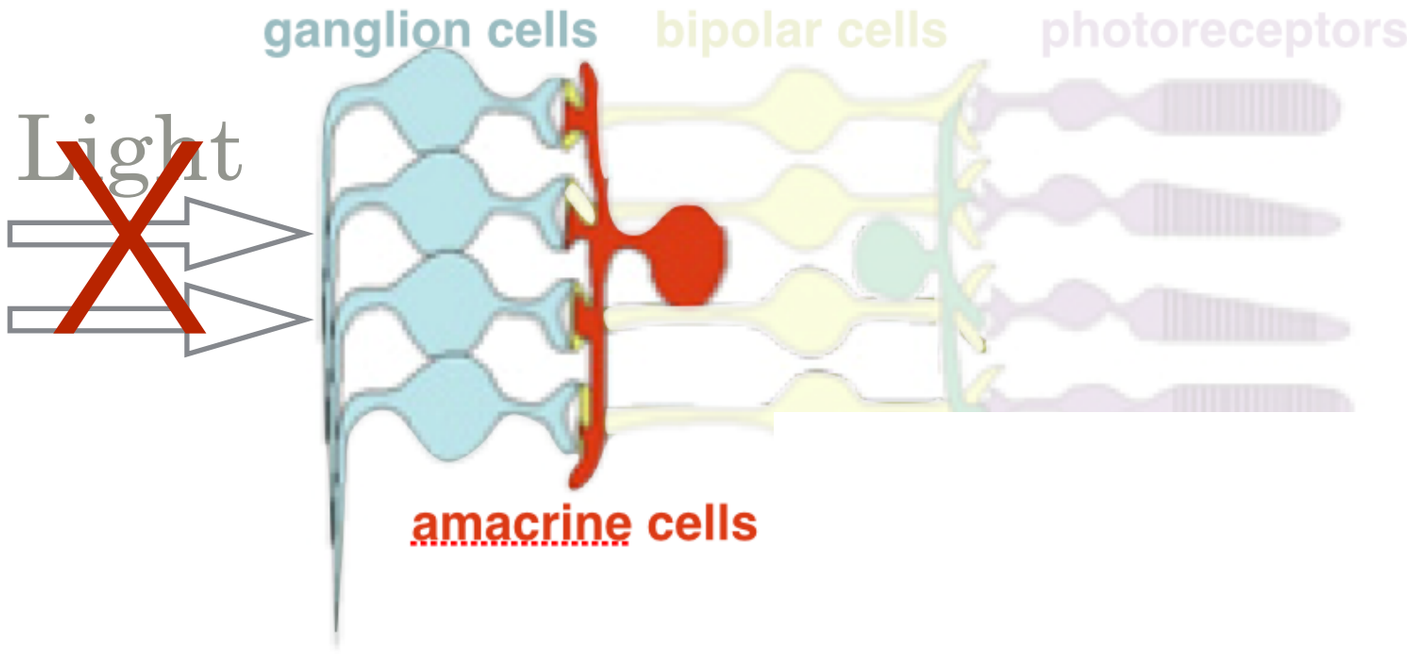
The structure of the retina during development

Retina's layered structure is shaped during development



The structure of the retina during development

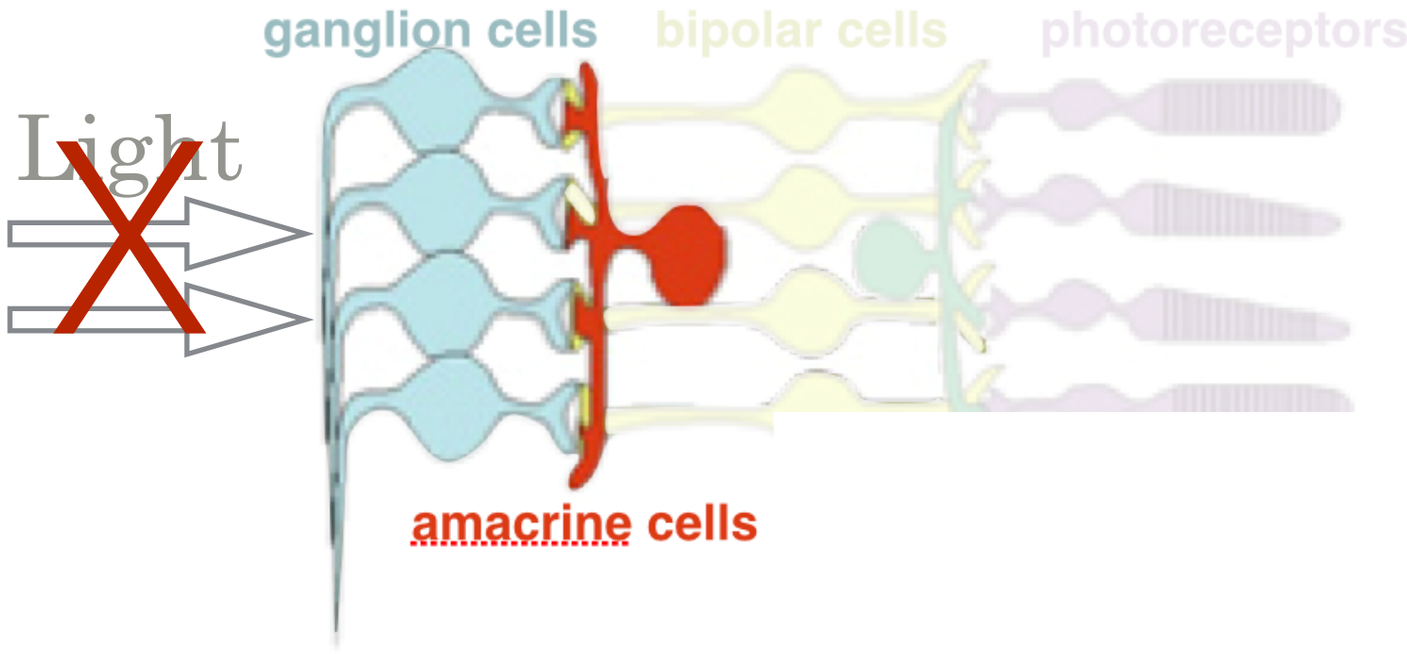
Retina's layered structure
is shaped during development



But How?

The structure of the retina during development

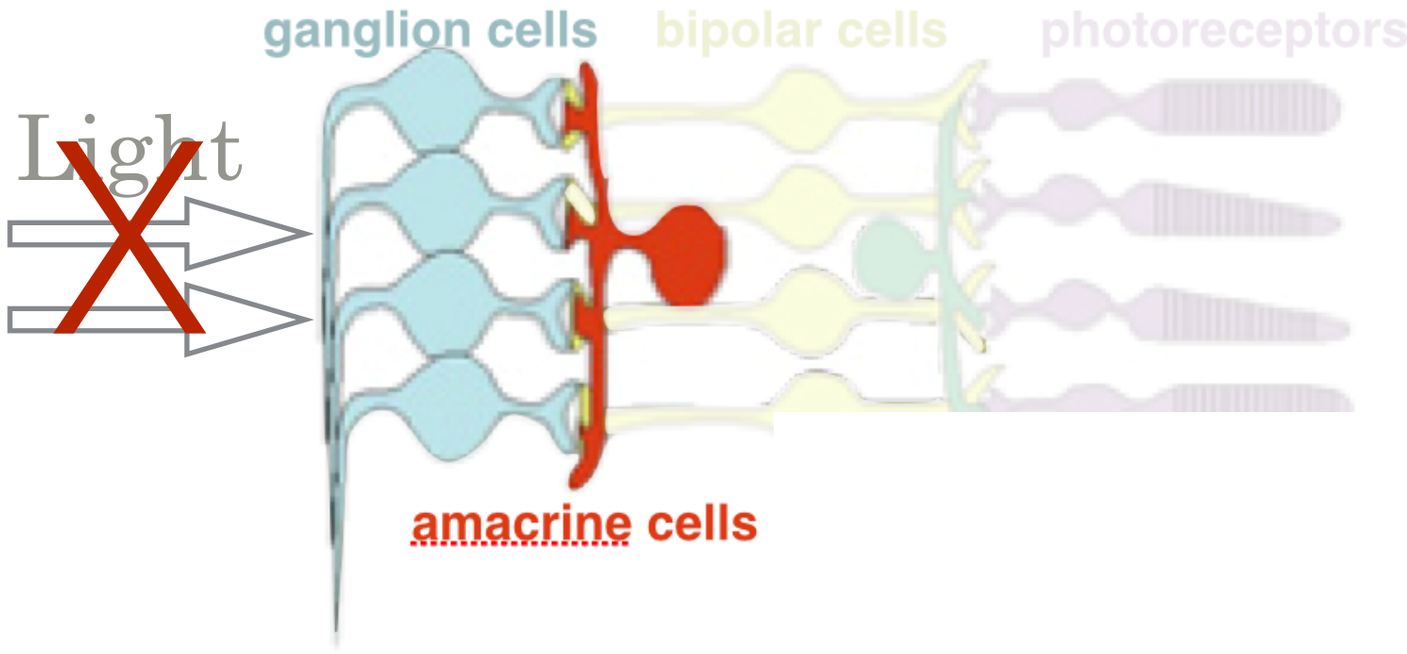
Retina's layered structure is shaped during development



But How? ⇨

The structure of the retina during development

Retina's layered structure is shaped during development



But How? → **Retinal waves!**

What are Retinal waves?

What are Retinal waves?

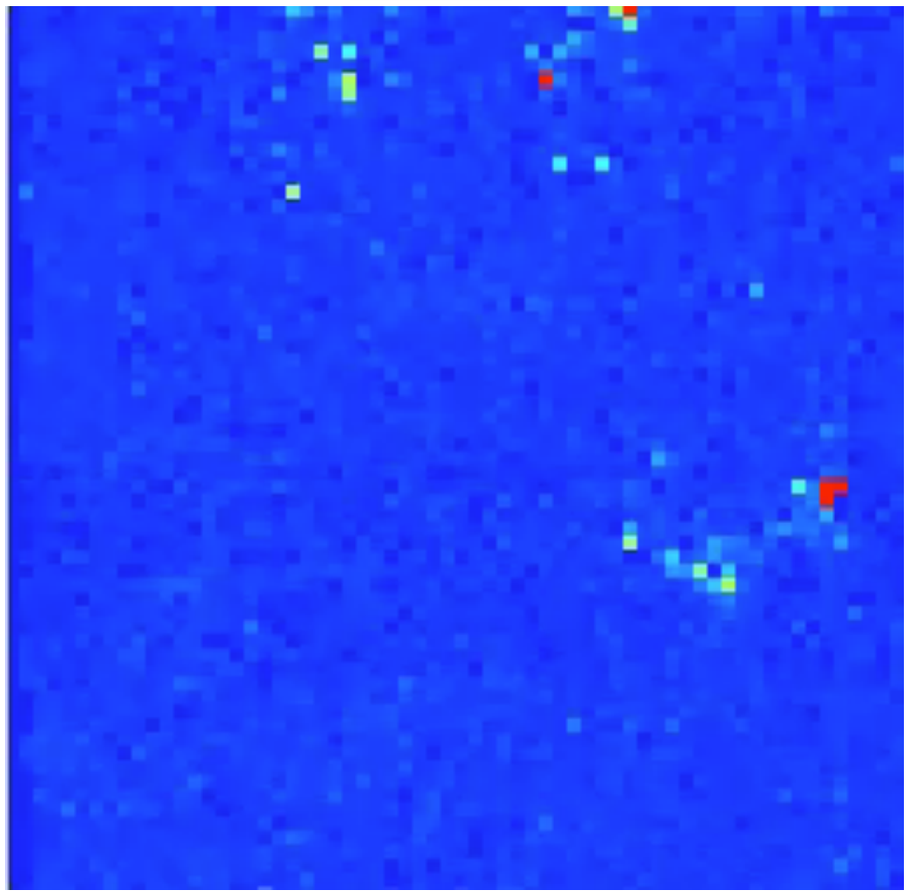
Spontaneous spatio-temporal waves during development

Disappear short after birth when vision is functional

What are Retinal waves?

Spontaneous spatio-temporal waves during development

Disappear short after birth when vision is functional



(Maccione et al. 2014)

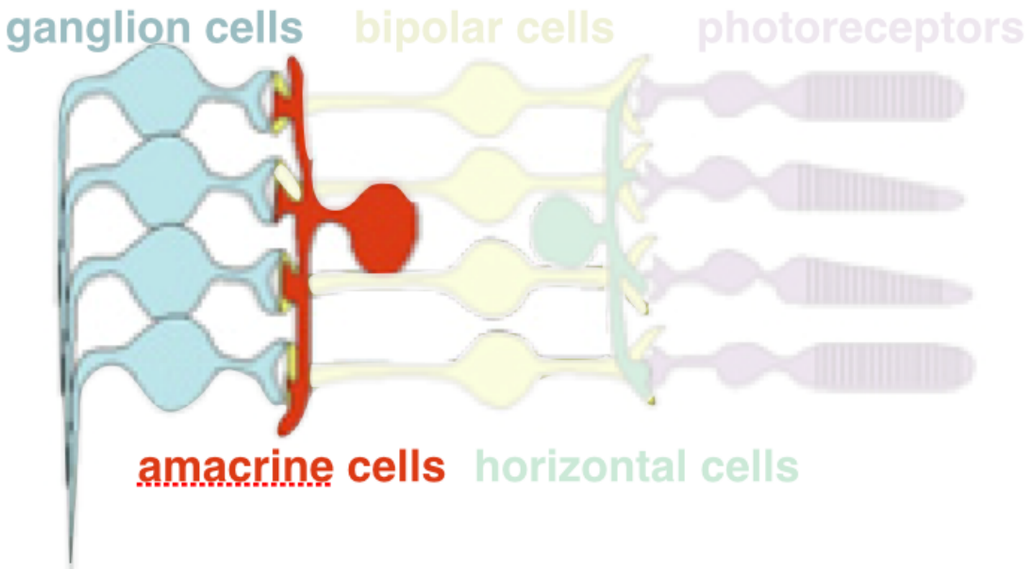
MEA recording of the voltage from a P11 mouse retina in the presence of 10 μM bicuculline.

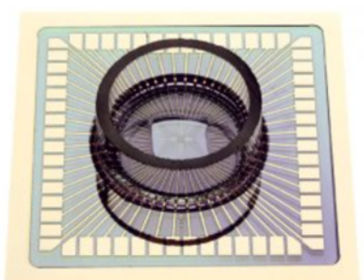
What are Retinal waves?

Spontaneous spatio-temporal waves during development

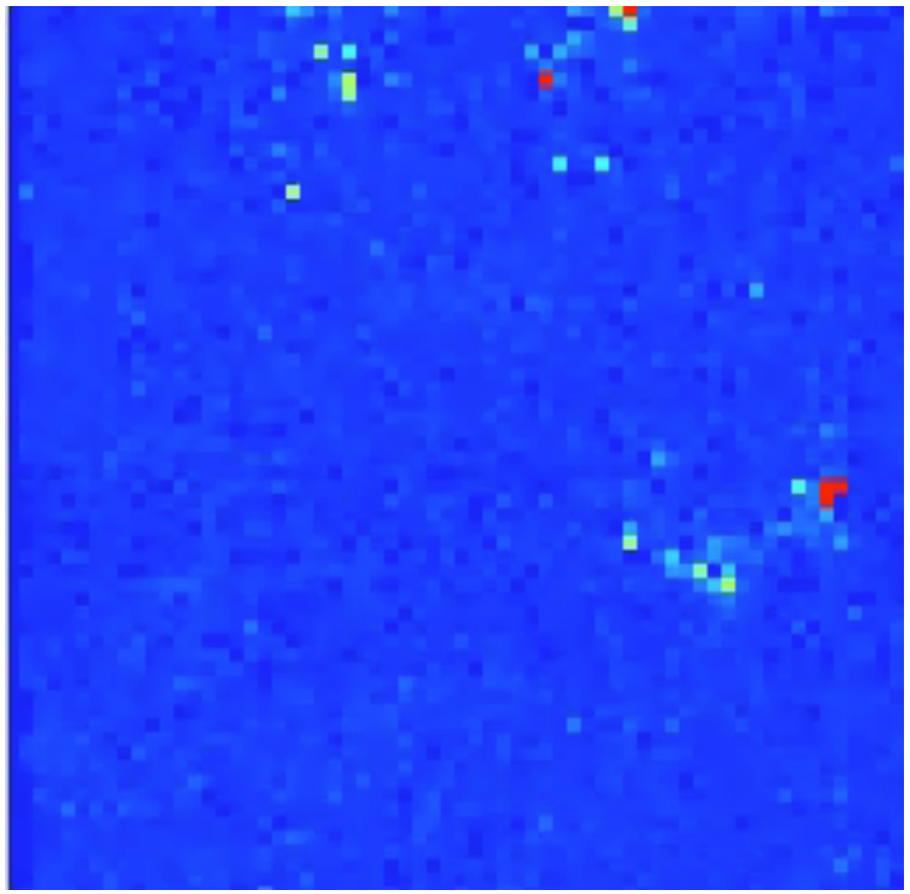
Disappear short after birth when vision is functional

Recordings from the retina





Multi-electrode array (MEA)



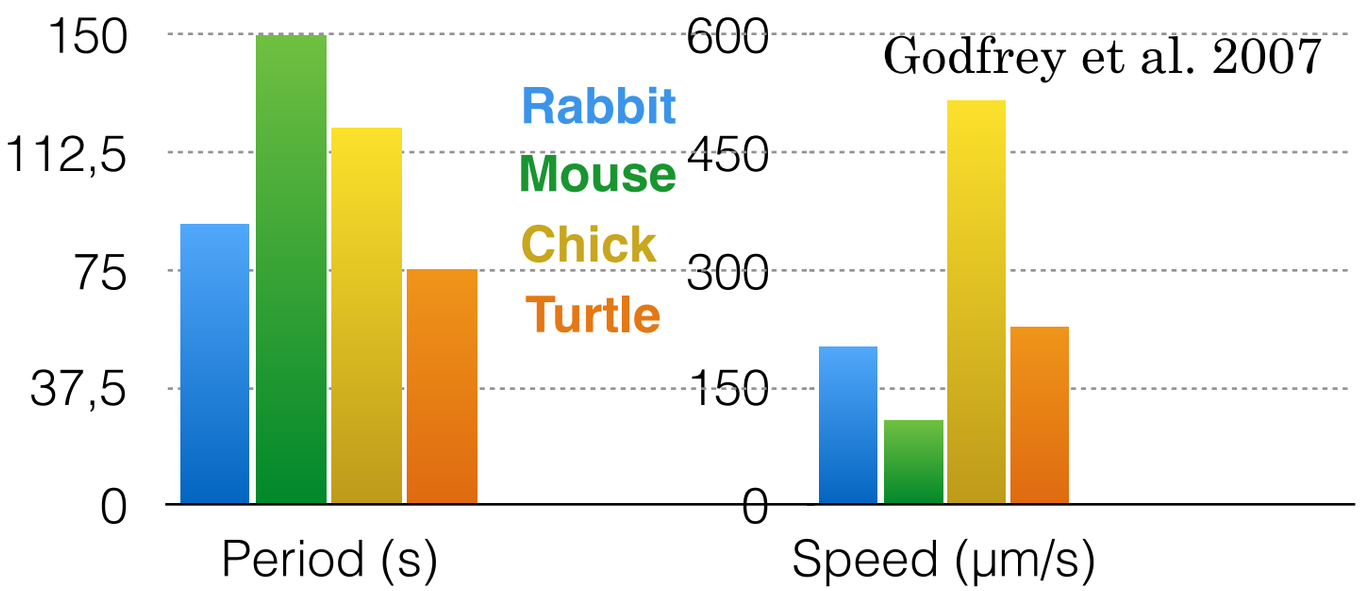
(Maccione et al. 2014)

MEA recording of the voltage from a P11 mouse retina in the presence of 10 μM bicuculline.

Variability <u>within</u> retinal waves

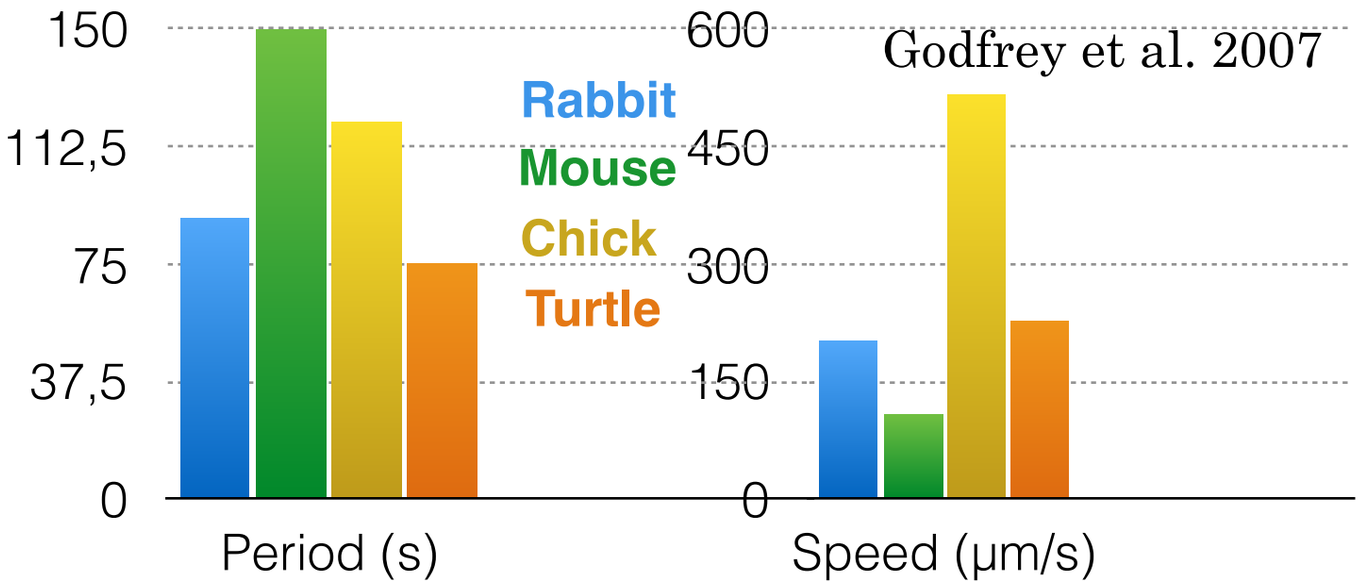
Variability within retinal waves

i) Across species

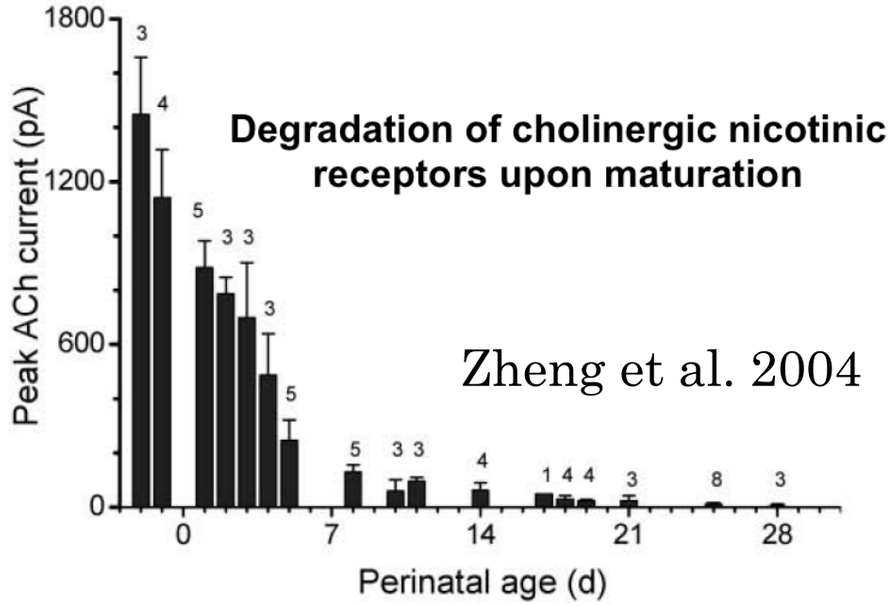


Variability within retinal waves

i) Across species

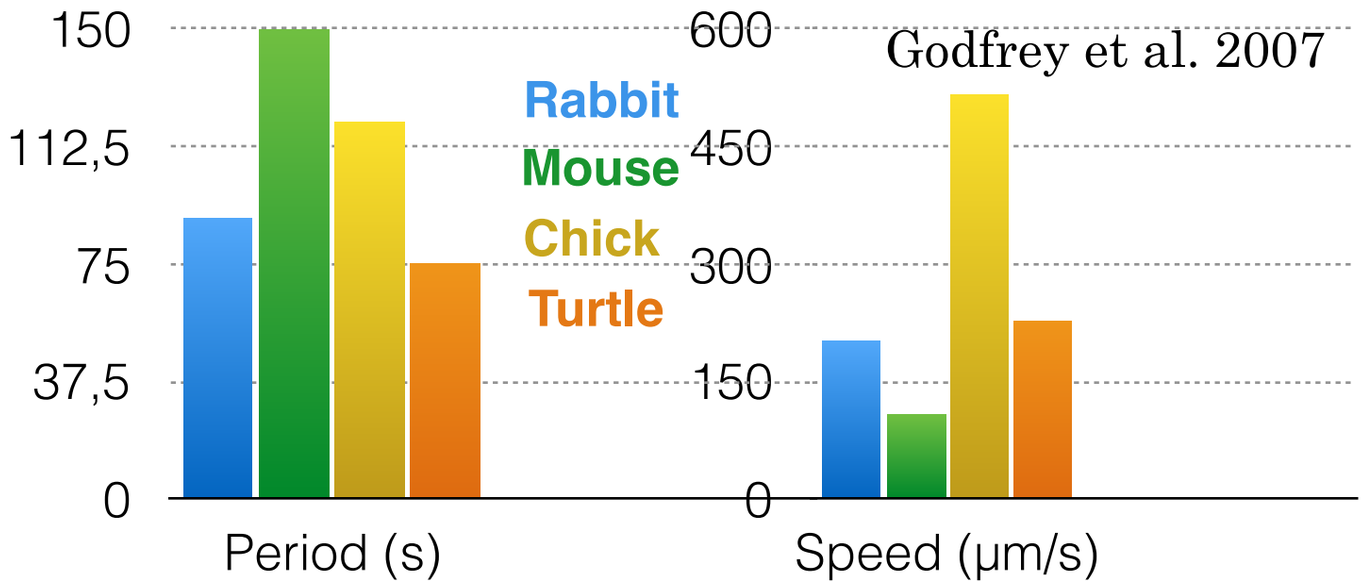


ii) Development

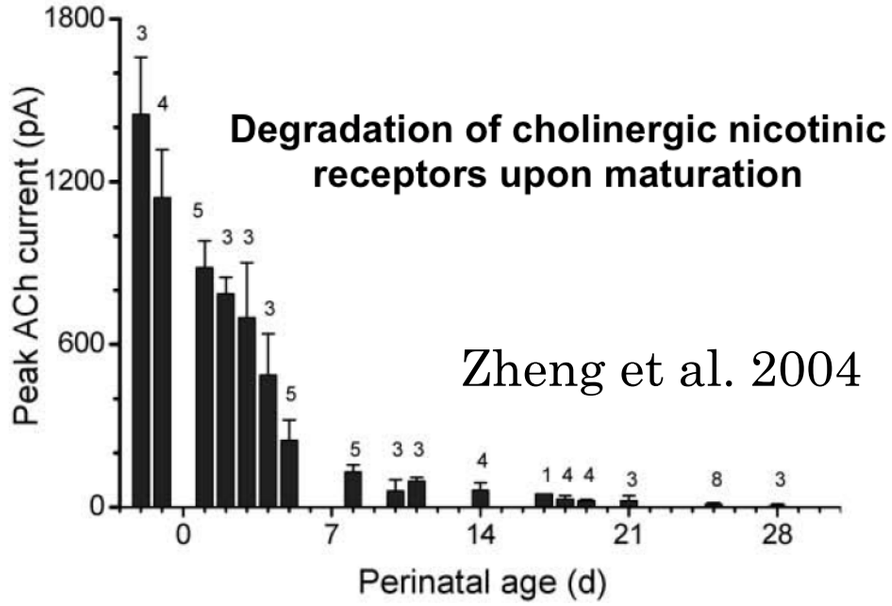


Variability within retinal waves

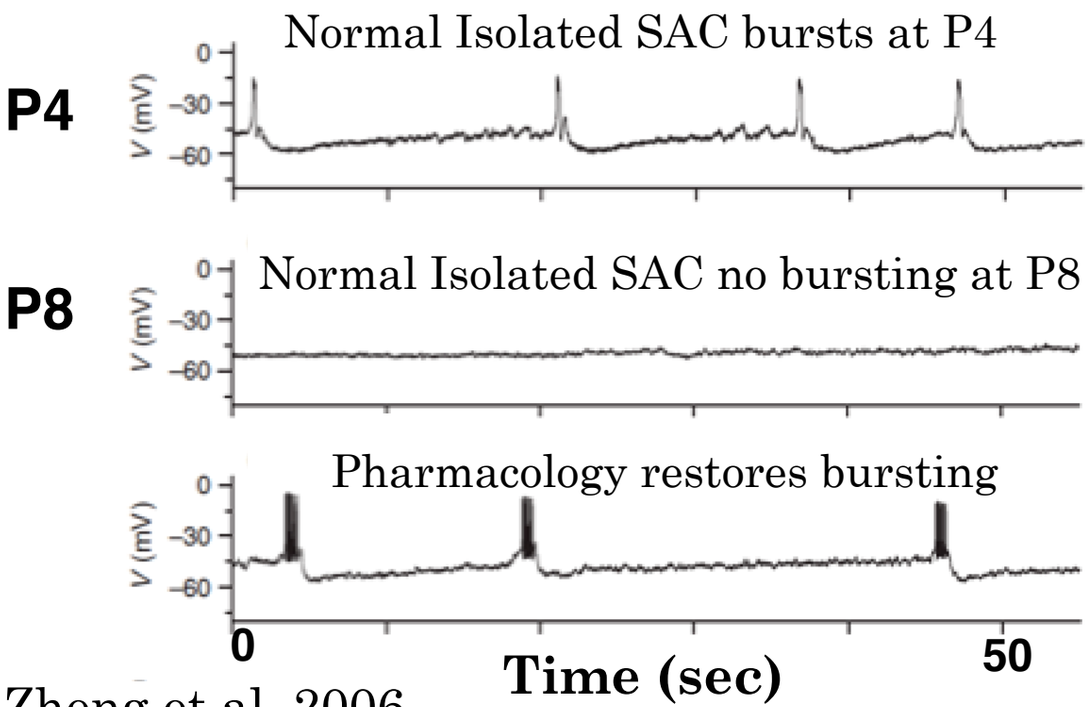
i) Across species



ii) Development



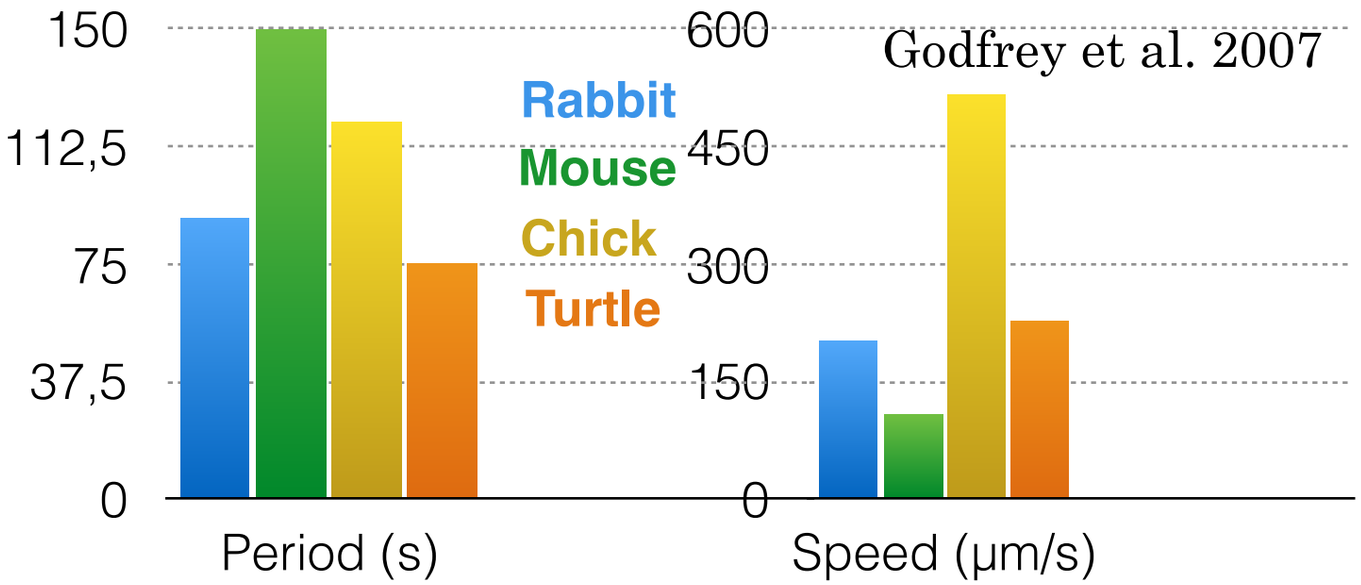
iii) Pharmacology



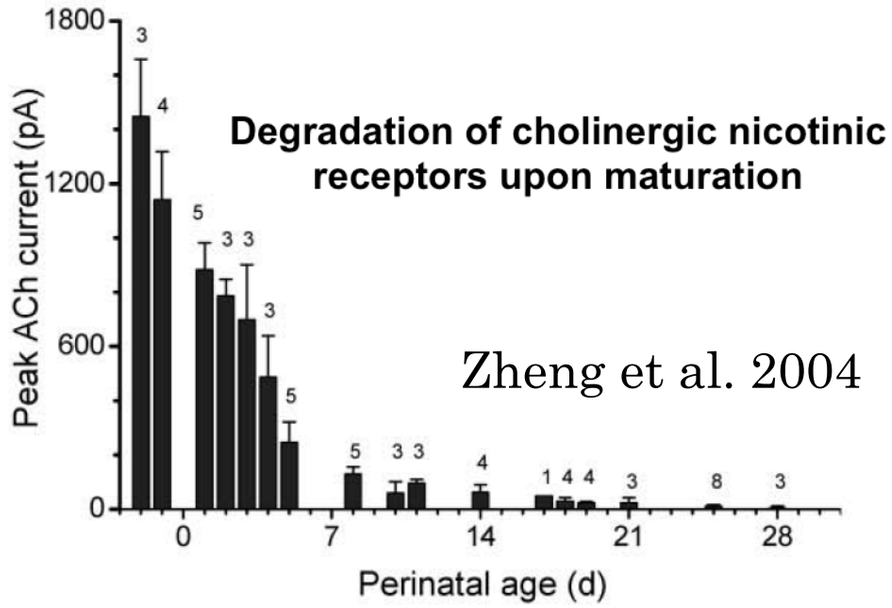
Zheng et al. 2006

Variability within retinal waves

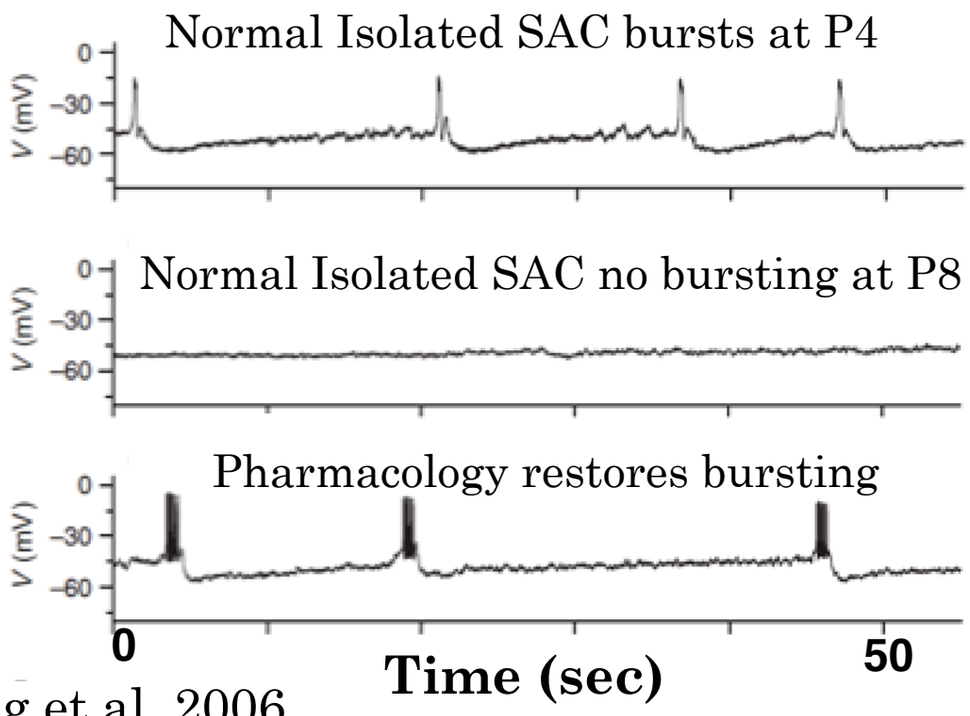
i) Across species



ii) Development

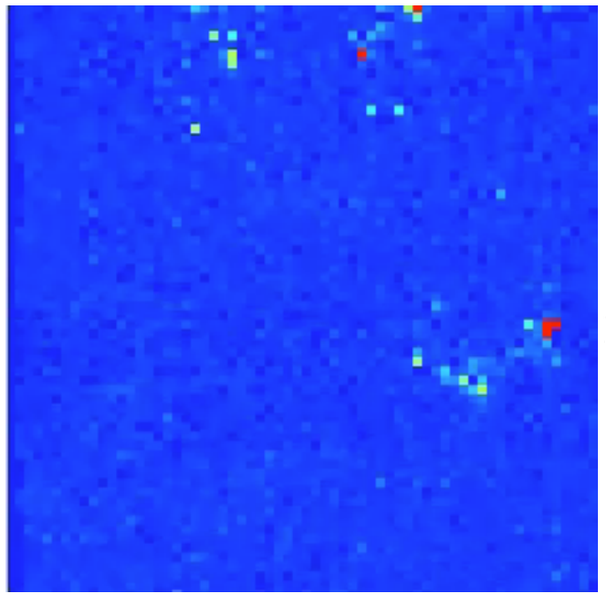


iii) Pharmacology



Zheng et al. 2006

iv) Spatial Variability



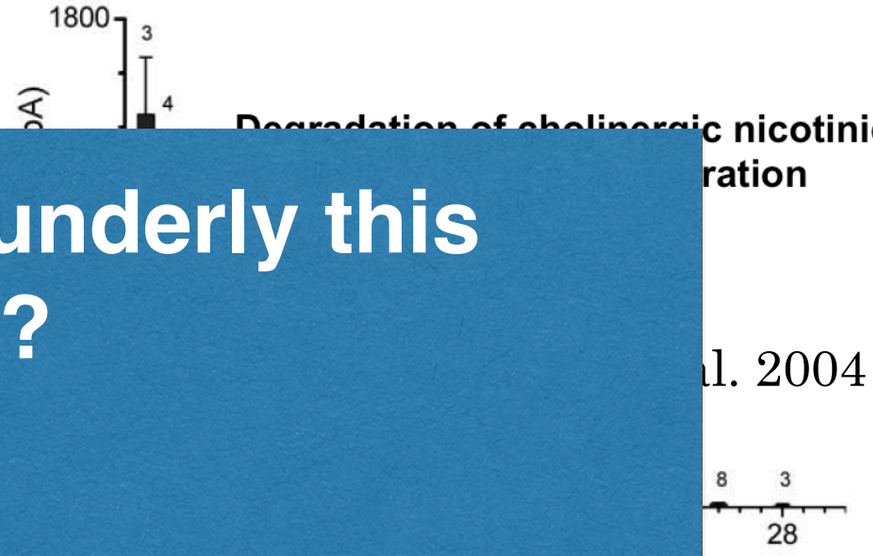
Maccione et al. 2014

Waves have variable shapes due to a refractory mechanism which controls their borders.

Variability within retinal waves

i) Across species

ii) Development



Degradation of cholinergic nicotinic ration

l. 2004

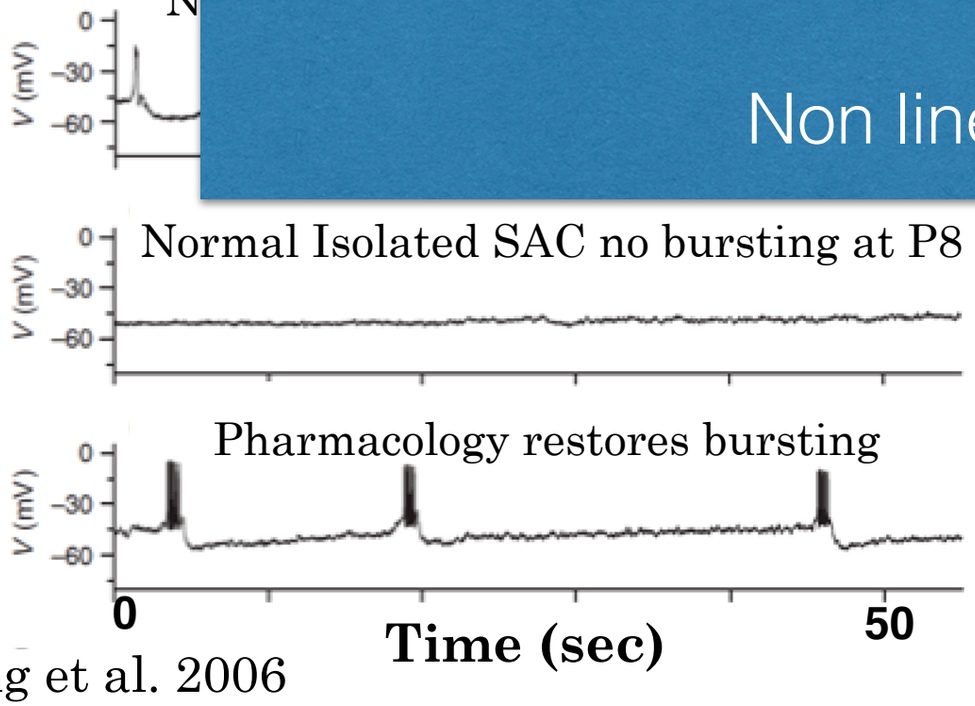
Which mechanisms underly this variability ?

Randomness ?

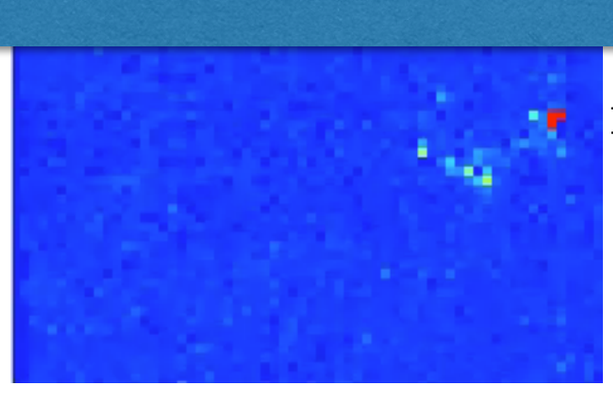
Genetics ?

Non linear dynamics ?

iii) ability



Zheng et al. 2006



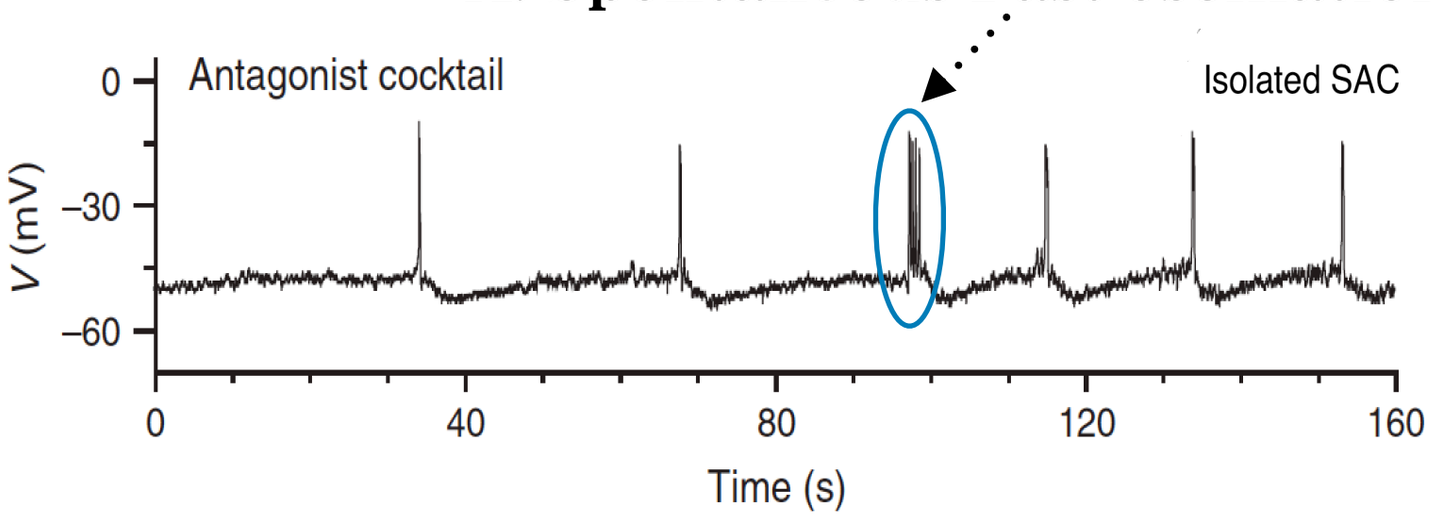
Maccione et al. 2014

have variable shapes due to a refractory mechanism which controls their borders.

Cellular mechanisms of SACs bursting

Cellular mechanisms of SACs bursting

A. Spontaneous Fast oscillations

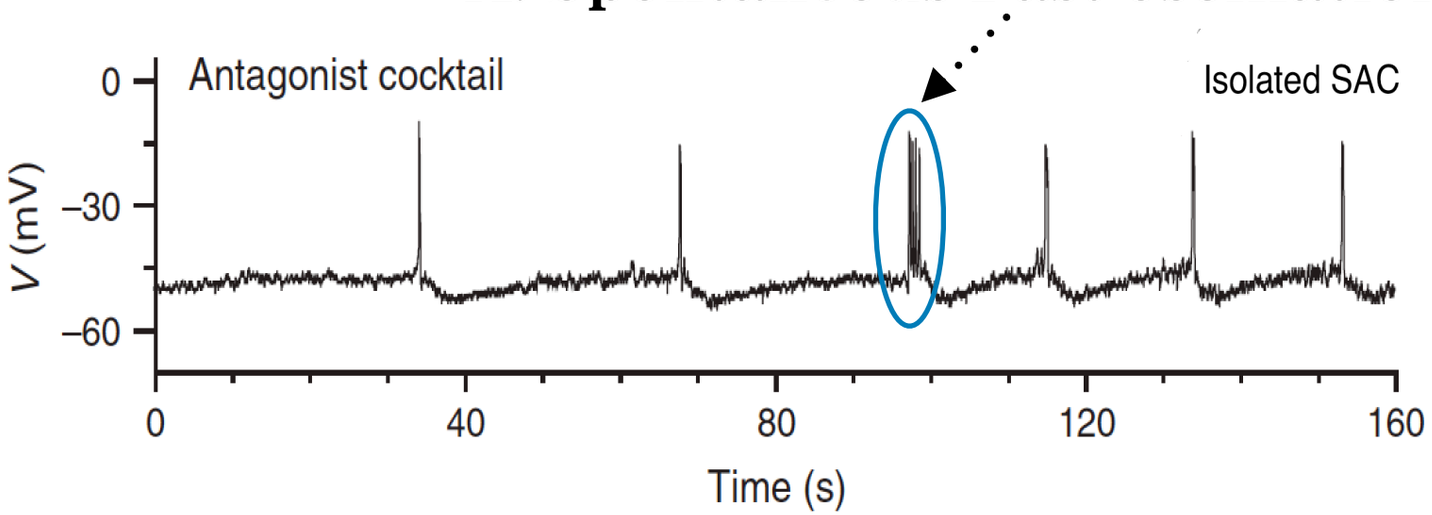


Generated mainly by <u>fast</u> voltage-gated Ca2+ channels

Zheng et al. 2006

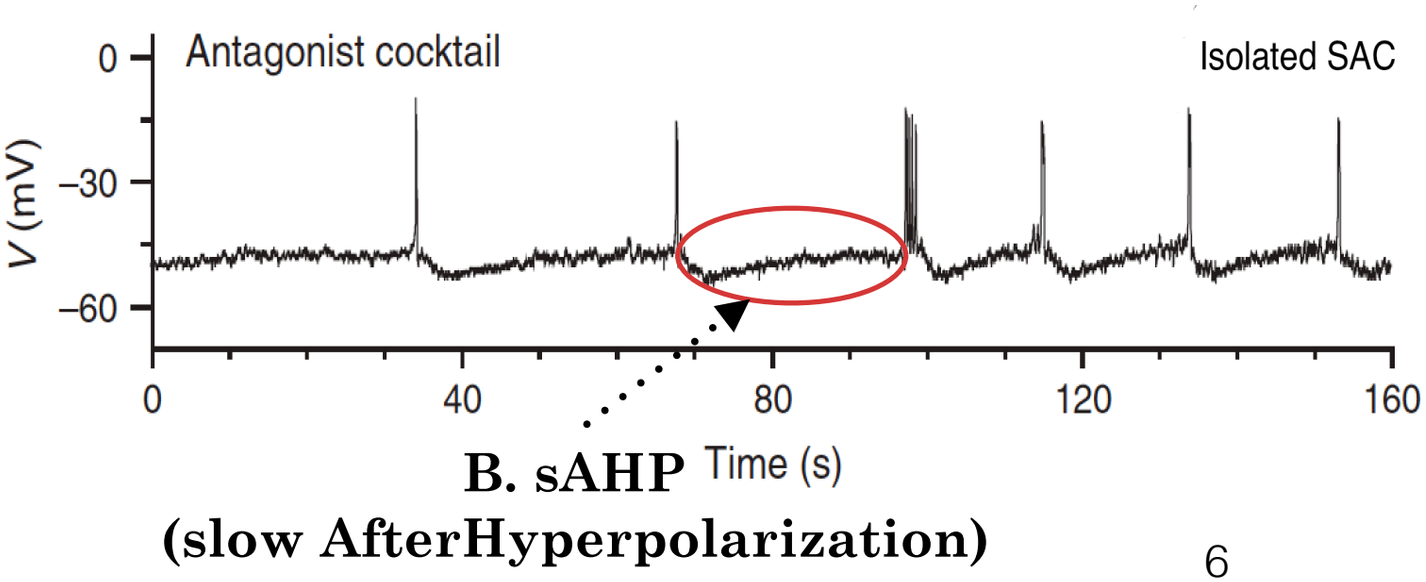
Cellular mechanisms of SACs bursting

A. Spontaneous Fast oscillations



Generated mainly by <u>fast</u> voltage-gated Ca2+ channels

Zheng et al. 2006



B. sAHP
(slow AfterHyperpolarization)

Generated mainly by <u>slow</u> Ca2+-gated K+ channels

Zheng et al. 2006

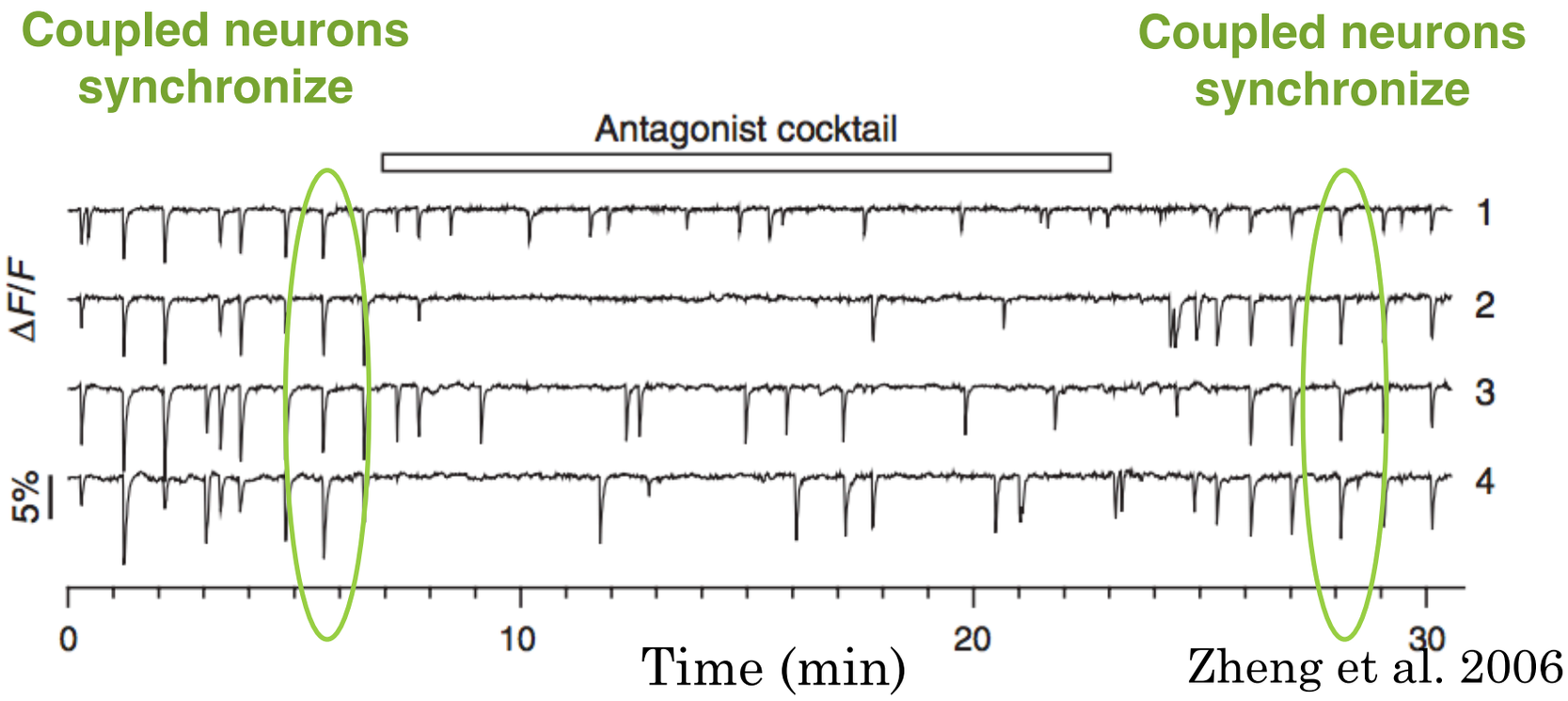
Cellular mechanisms of stage II retinal waves

Cellular mechanisms of stage II retinal waves

C. Synchrony through Acetylcholine

Cellular mechanisms of stage II retinal waves

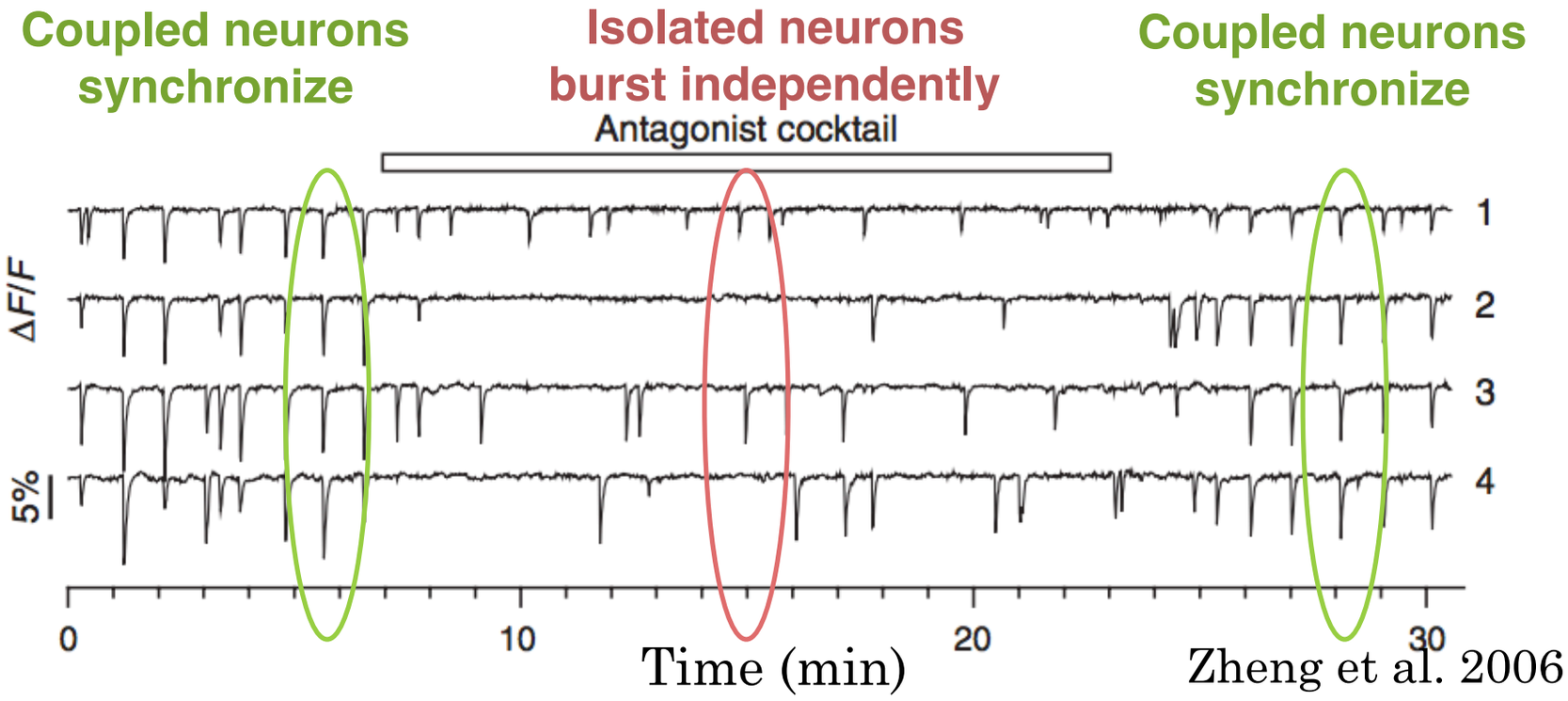
C. Synchrony through Acetylcholine



Zheng et al. 2006

Cellular mechanisms of stage II retinal waves

C. Synchrony through Acetylcholine



Zheng et al. 2006

Mutual excitatory connections between SACs through Acetylcholine

A network model for stage II retinal waves

$$
\begin{cases}
C_m \frac{dV_i}{dt} &= -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\
&\quad - G_{sAHP}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k\in\mathcal{B}_i})(V_i - V_A) \\
\tau_N \frac{dN_i}{dt} &= \Lambda(V_i)(N_\infty(V_i) - N_i) \\
\tau_C \frac{dC_i}{dt} &= -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\
\tau_S \frac{dS_i}{dt} &= \alpha_S(1 - S_i)C_i^4 - S_i \\
\tau_R \frac{dR_i}{dt} &= \alpha_R S_i(1 - R_i) - R_i \\
\frac{dA_i}{dt} &= -\mu A_i + \beta_A T_A(V_i),
\end{cases}
$$

A network model for stage II retinal waves

N neurons, 6 N equations

~ 20 parameters per neuron

Tuned to match experimental records.

$$
\begin{cases}
C_m \frac{dV_i}{dt} &= -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\
&\quad - G_{sAHP}(R_i)(V_i - V_K) - G_A(\{A_i\}_{\text{neigh}})(V_i - V_A) \\
\tau_N \frac{dN_i}{dt} &= \Lambda(V_i)(N_\infty(V_i) - N_i) \\
\tau_C \frac{dC_i}{dt} &= -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\
\tau_S \frac{dS_i}{dt} &= \alpha_S(1 - S_i)C_i^4 - S_i \\
\tau_R \frac{dR_i}{dt} &= \alpha_R S_i(1 - R_i) - R_i \\
\frac{dA_i}{dt} &= -\mu A_i + \beta_A T_A(V_i),
\end{cases}
$$

A network model for stage II retinal waves

N neurons, 6 N equations

$$
\begin{cases}
C_m \frac{dV_i}{dt} &= -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\
&\quad - G_{sAHP}(R_i)(V_i - V_K) - G_A(\{A_i\}_{\text{neigh}})(V_i - V_A) \\
\tau_N \frac{dN_i}{dt} &= \Lambda(V_i)(N_\infty(V_i) - N_i) \\
\tau_C \frac{dC_i}{dt} &= -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\
\tau_S \frac{dS_i}{dt} &= \alpha_S(1 - S_i)C_i^4 - S_i \\
\tau_R \frac{dR_i}{dt} &= \\
\frac{dA_i}{dt} &=
\end{cases}
$$

~ 20 parameters per neuron

Tuned to match experimental records.

Time scale separation

Fast $V, N.$ $\tau_L = 11$ ms, $\tau_N = 5$ ms.

Medium $C, A.$ $\tau_C = 2$ s, $\tau_A = 1.86$ s.

Slow $S, R.$ $\tau_R = \tau_S = 44$ s.

A network model for stage II retinal waves

$$
\begin{cases}
C_m \frac{dV_i}{dt} &= -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\
&\quad - G_{sAHP}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k\in\mathcal{B}_i})(V_i - V_A) \\
\tau_N \frac{dN_i}{dt} &= \Lambda(V_i)(N_\infty(V_i) - N_i) \\
\tau_C \frac{dC_i}{dt} &= -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\
\tau_S \frac{dS_i}{dt} &= \alpha_S(1 - S_i)C_i^4 - S_i \\
\tau_R \frac{dR_i}{dt} &= \alpha_R S_i(1 - R_i) - R_i \\
\frac{dA_i}{dt} &= -\mu A_i + \beta_A T_A(V_i),
\end{cases}
$$

A network model for stage II retinal waves

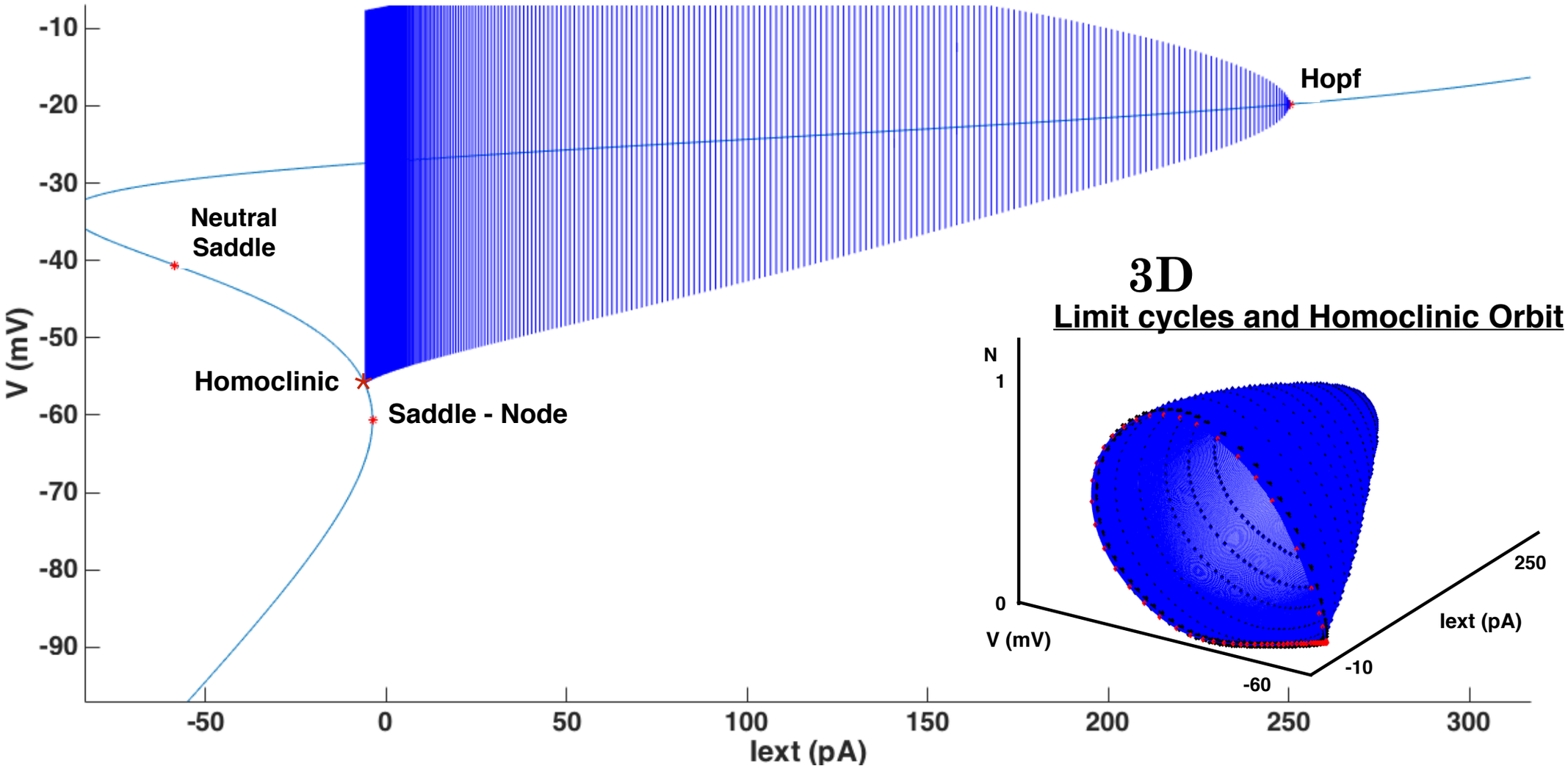
$$
\begin{aligned}
C_m \frac{dV_i}{dt} &= -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\
&\quad - G_{sAHP}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k\in\mathcal{B}_i})(V_i - V_A) \\
&\quad + I(R_i, A_j) \\
\tau_N \frac{dN_i}{dt} &= \Lambda(V_i)(N_\infty(V_i) - N_i) \\
\tau_C \frac{dC_i}{dt} &= -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\
\tau_S \frac{dS_i}{dt} &= \alpha_S(1 - S_i)C_i^4 - S_i \\
\tau_R \frac{dR_i}{dt} &= \alpha_R S_i(1 - R_i) - R_i \\
\frac{dA_i}{dt} &= -\mu A_i + \beta_A T_A(V_i),
\end{aligned}
$$

$I(R_i, A_j)$

Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

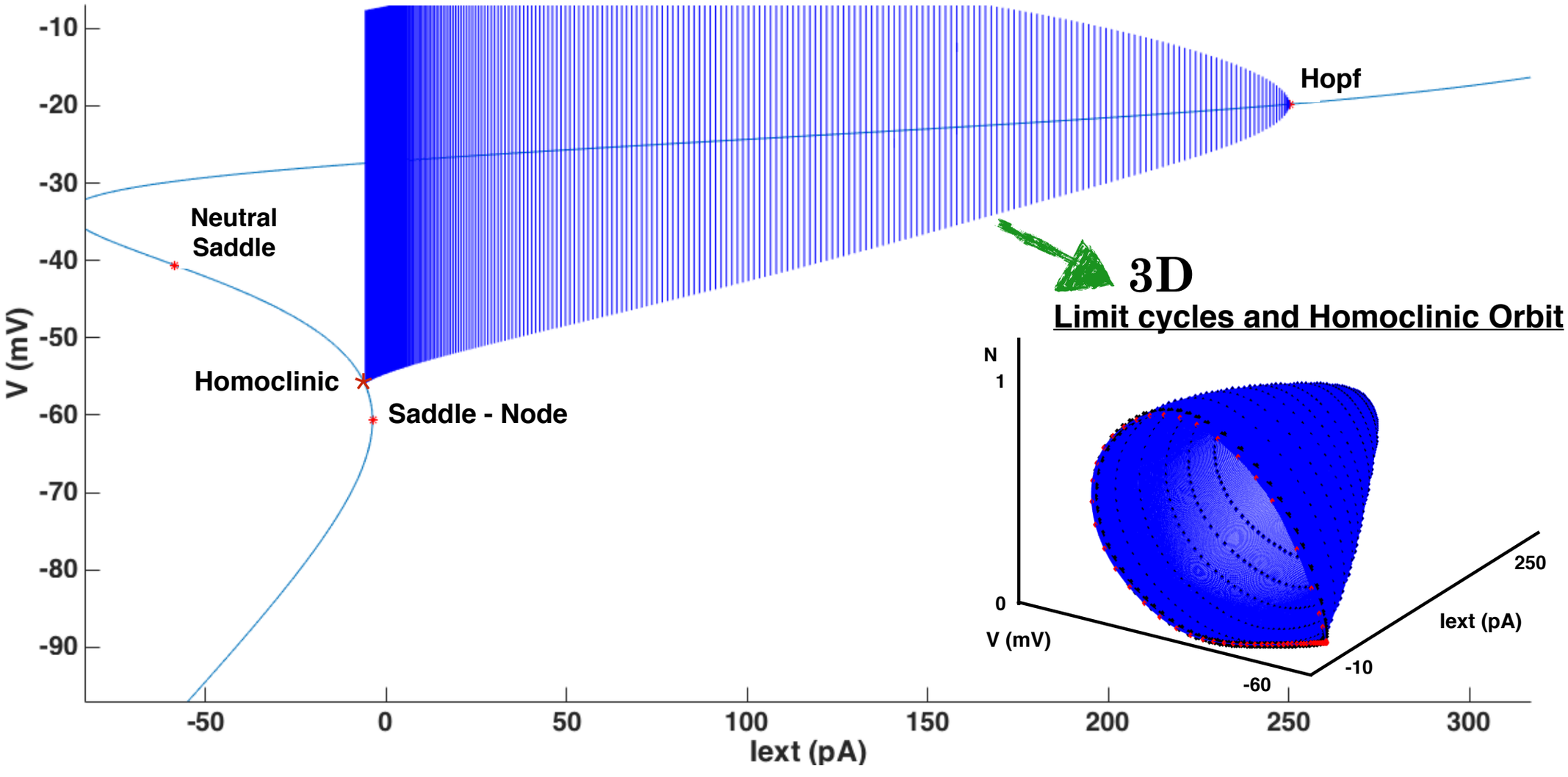
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

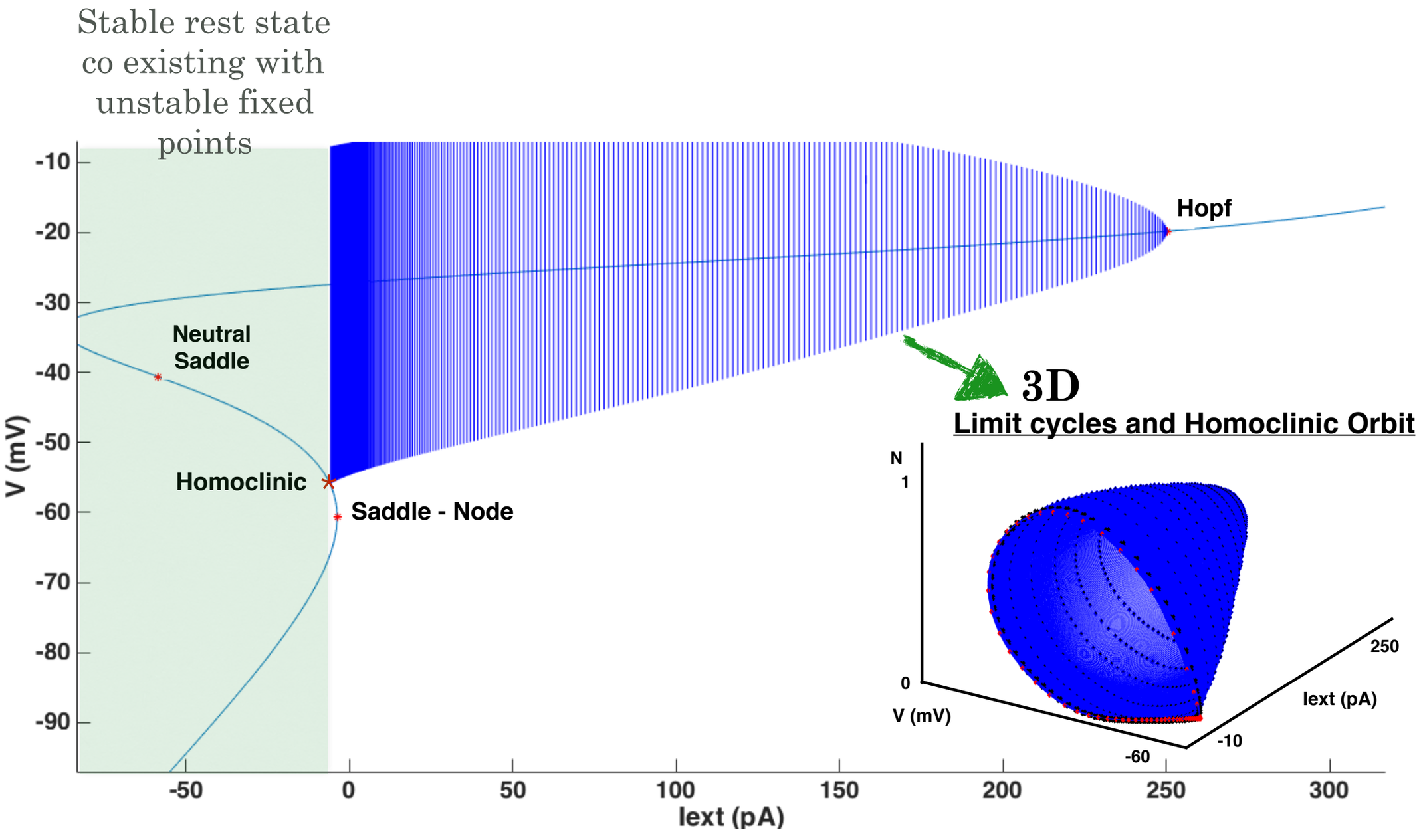
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

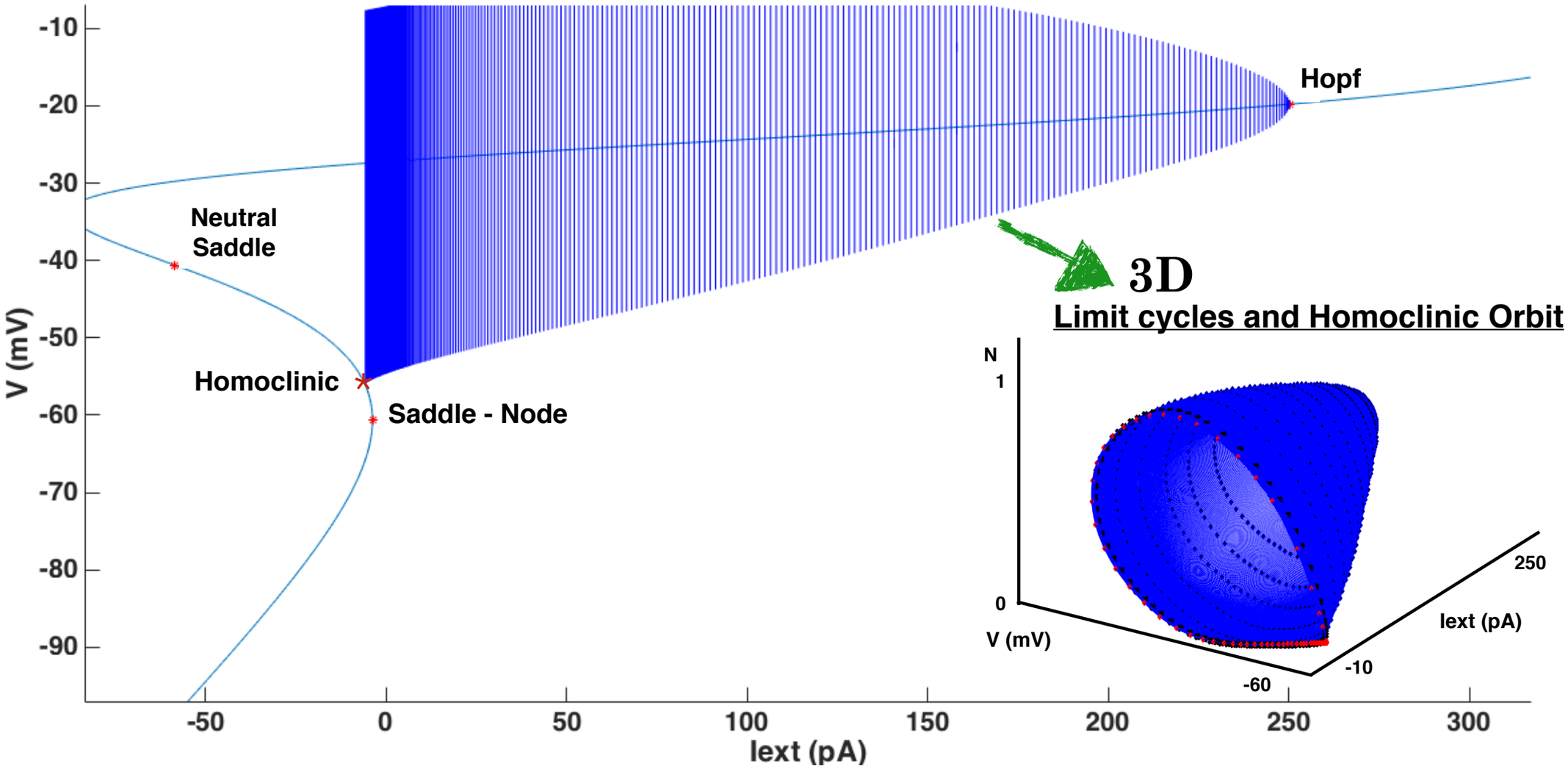
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

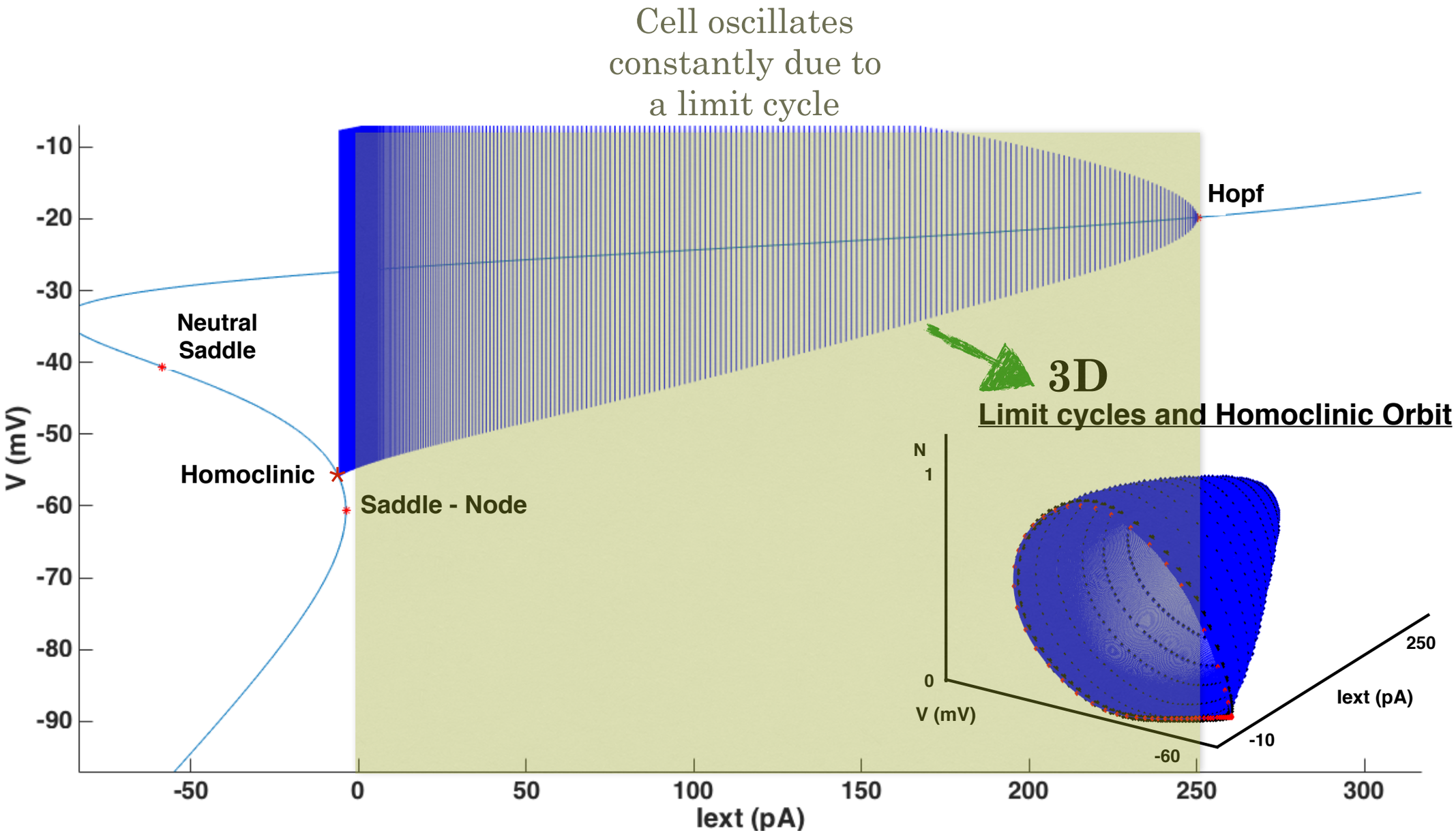
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

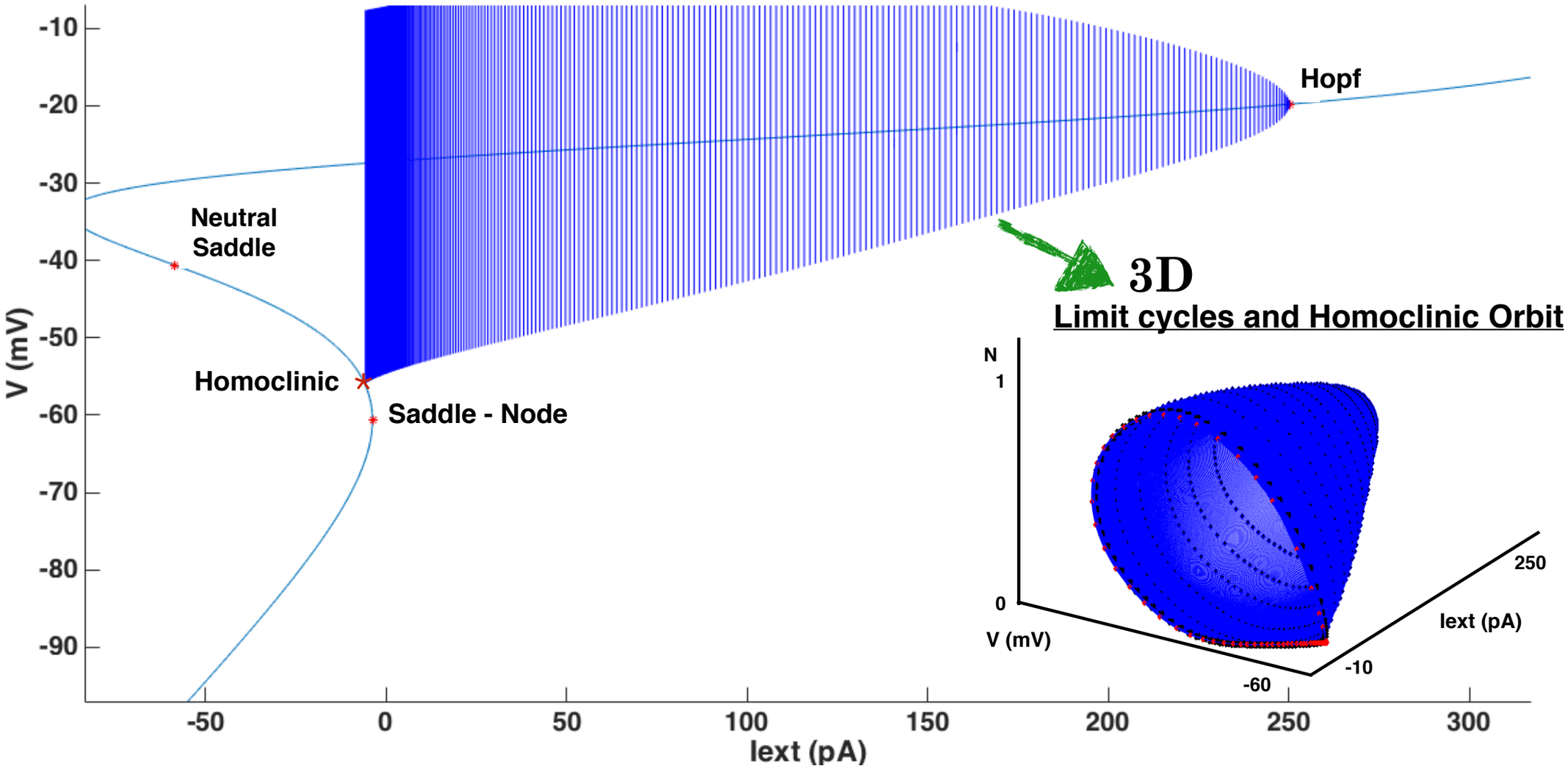
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

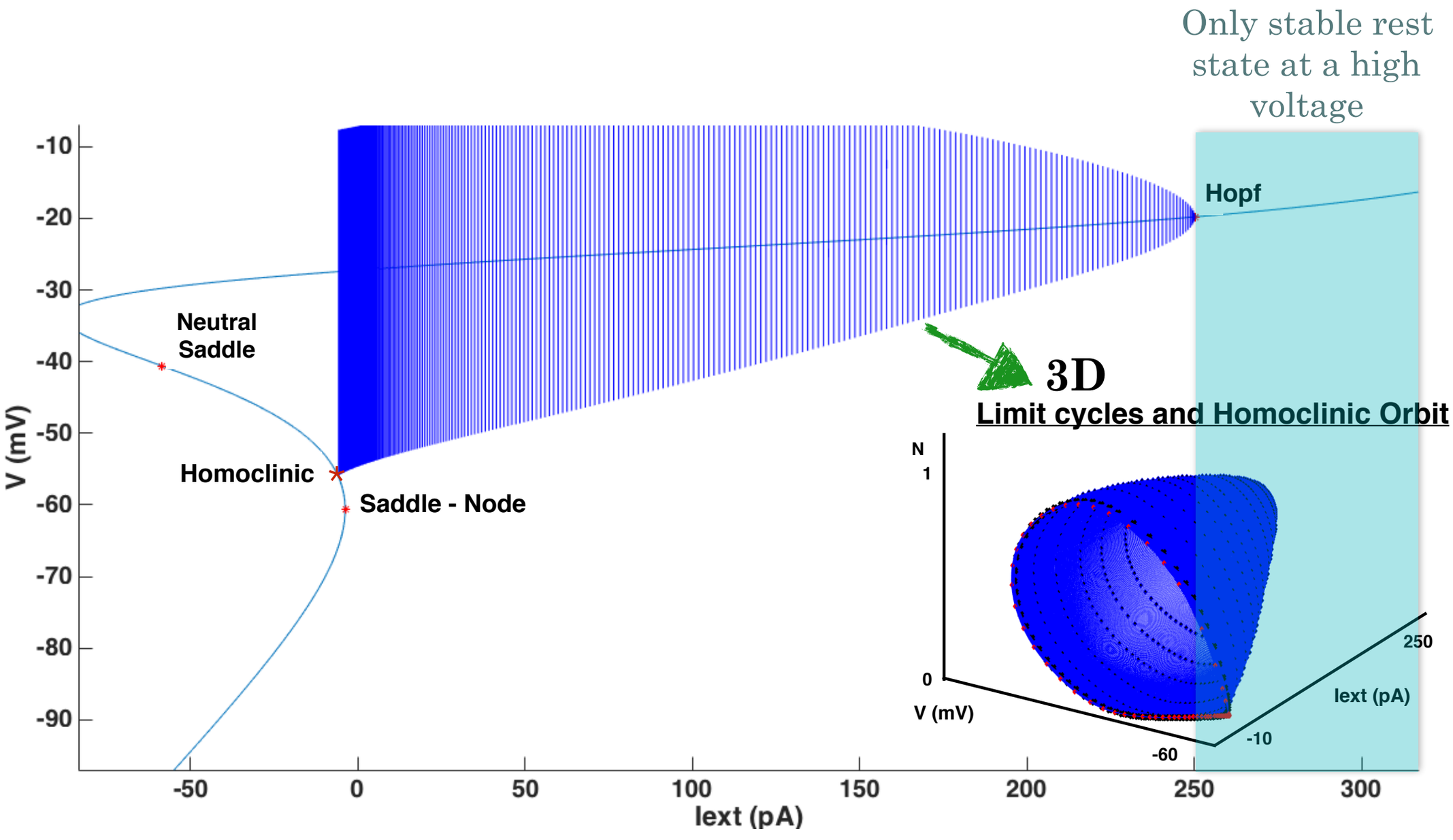
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

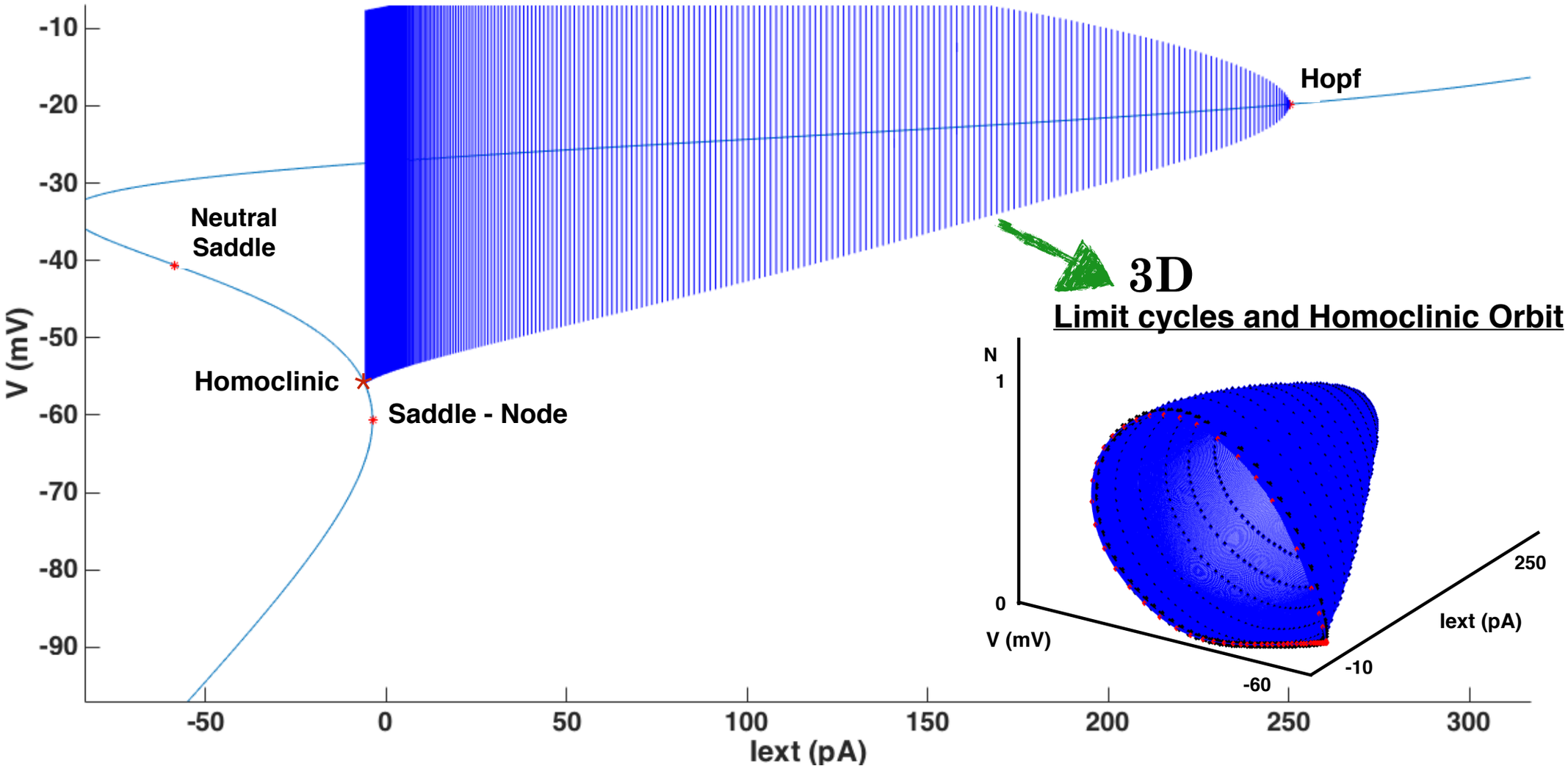
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

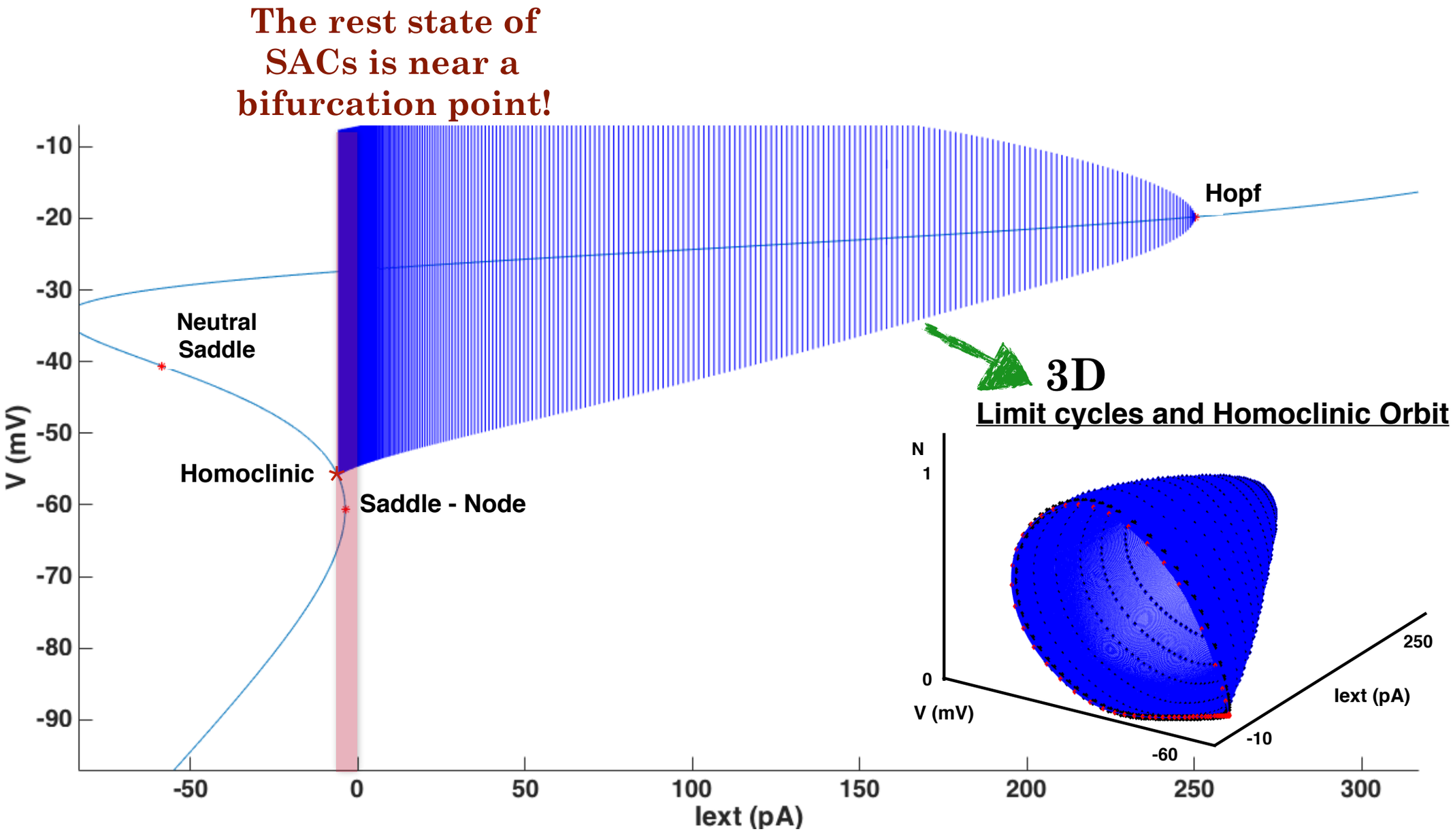
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

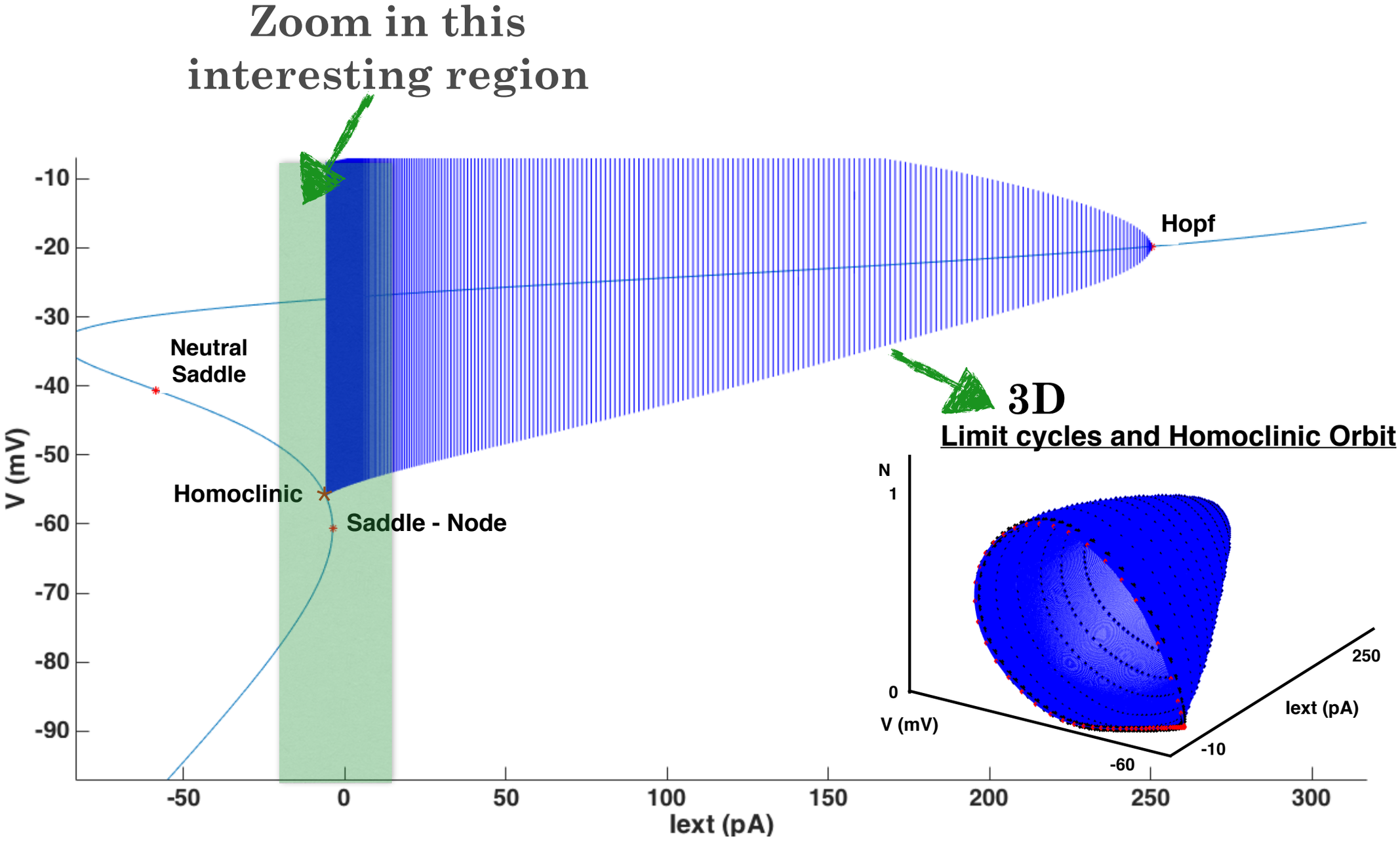
I. The SACs repertoire of dynamics upon a varying current



Bifurcation diagram of the fast subsystem (V,N)

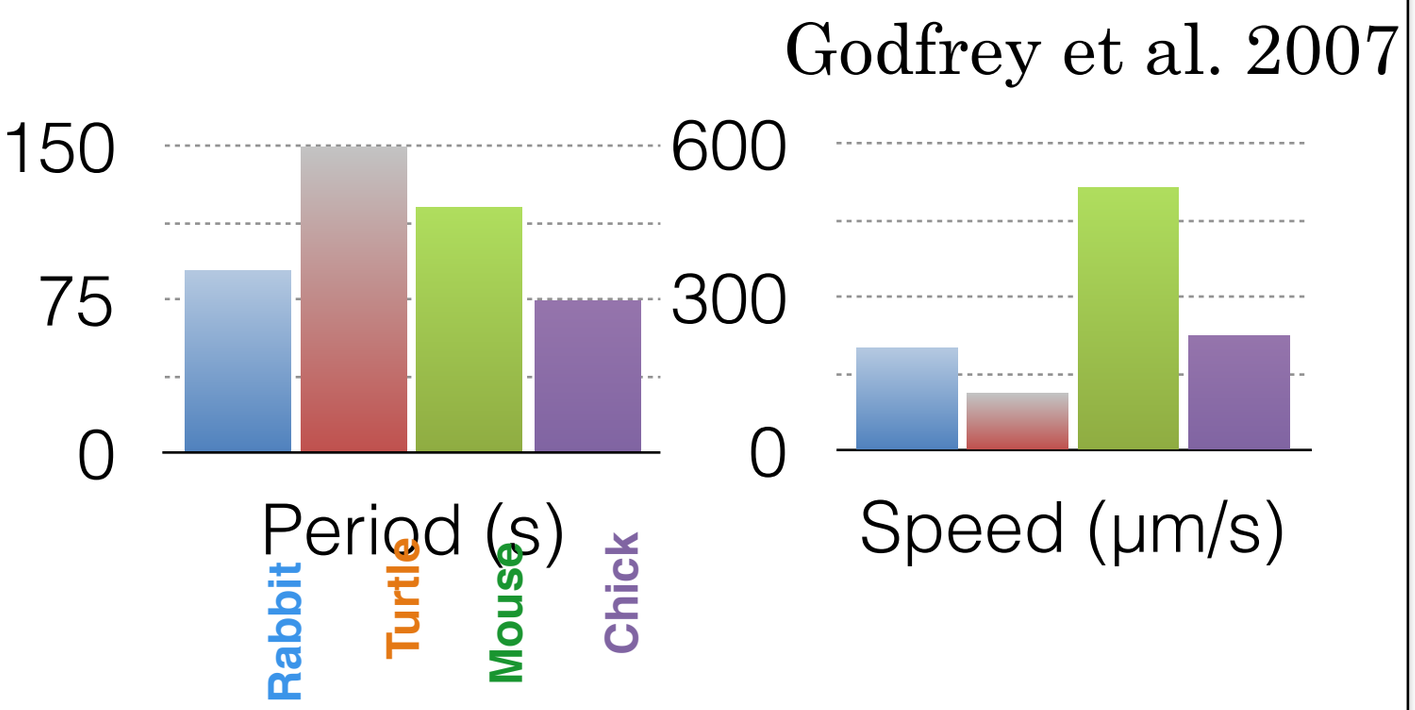
What do we learn about SACs?

I. The SACs repertoire of dynamics upon a varying current



Variability within retinal waves

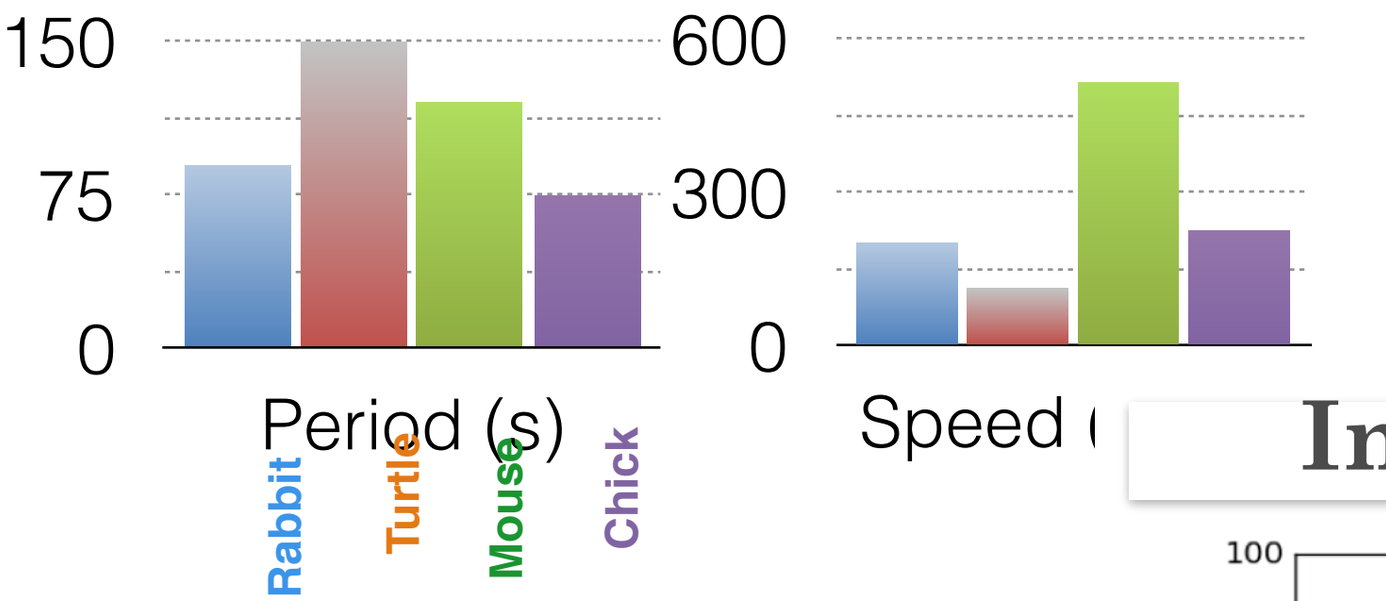
i) Across species



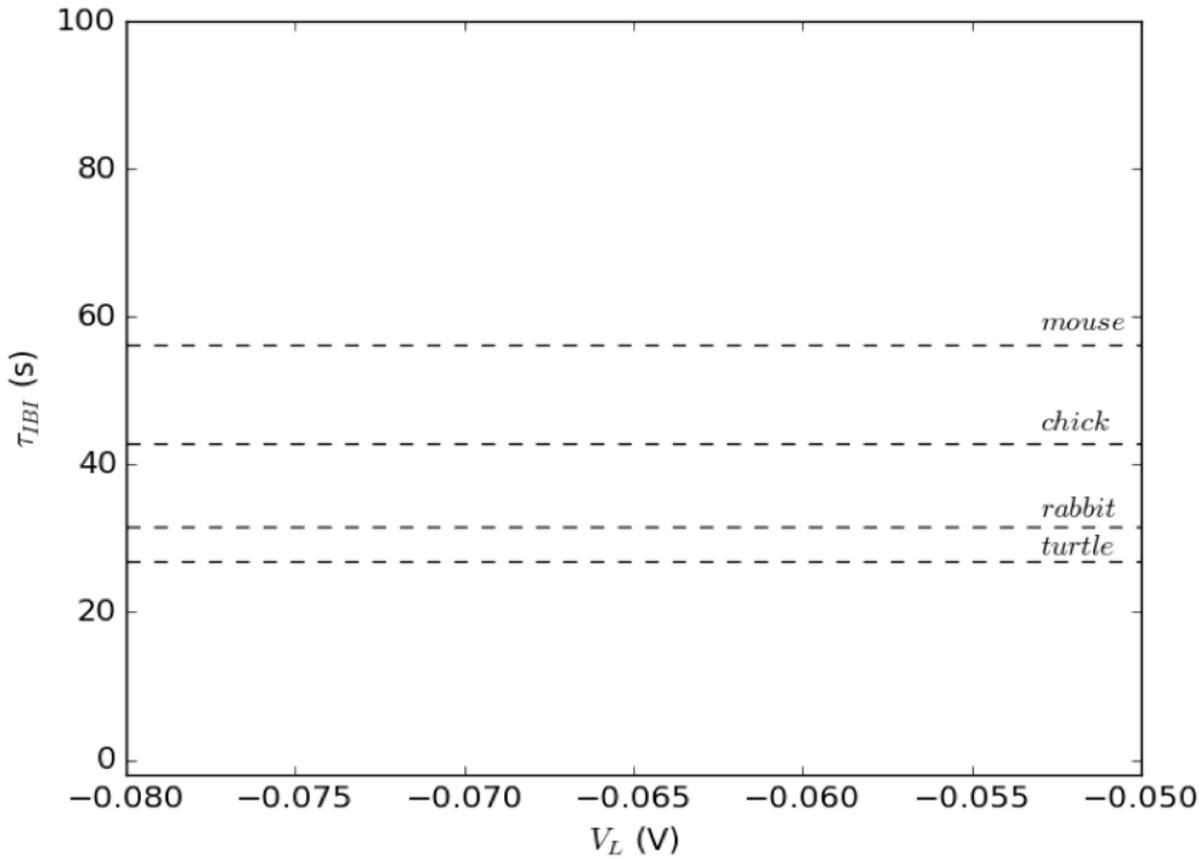
Variability within retinal waves

i) Across species

Godfrey et al. 2007



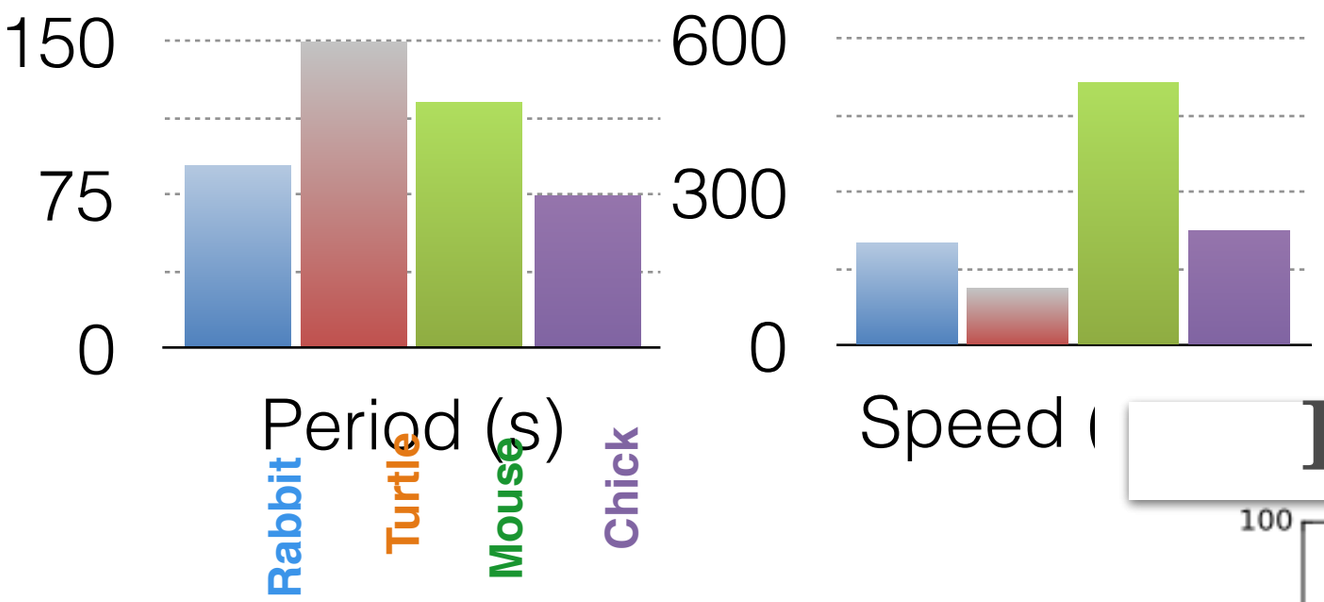
Interburst intervals



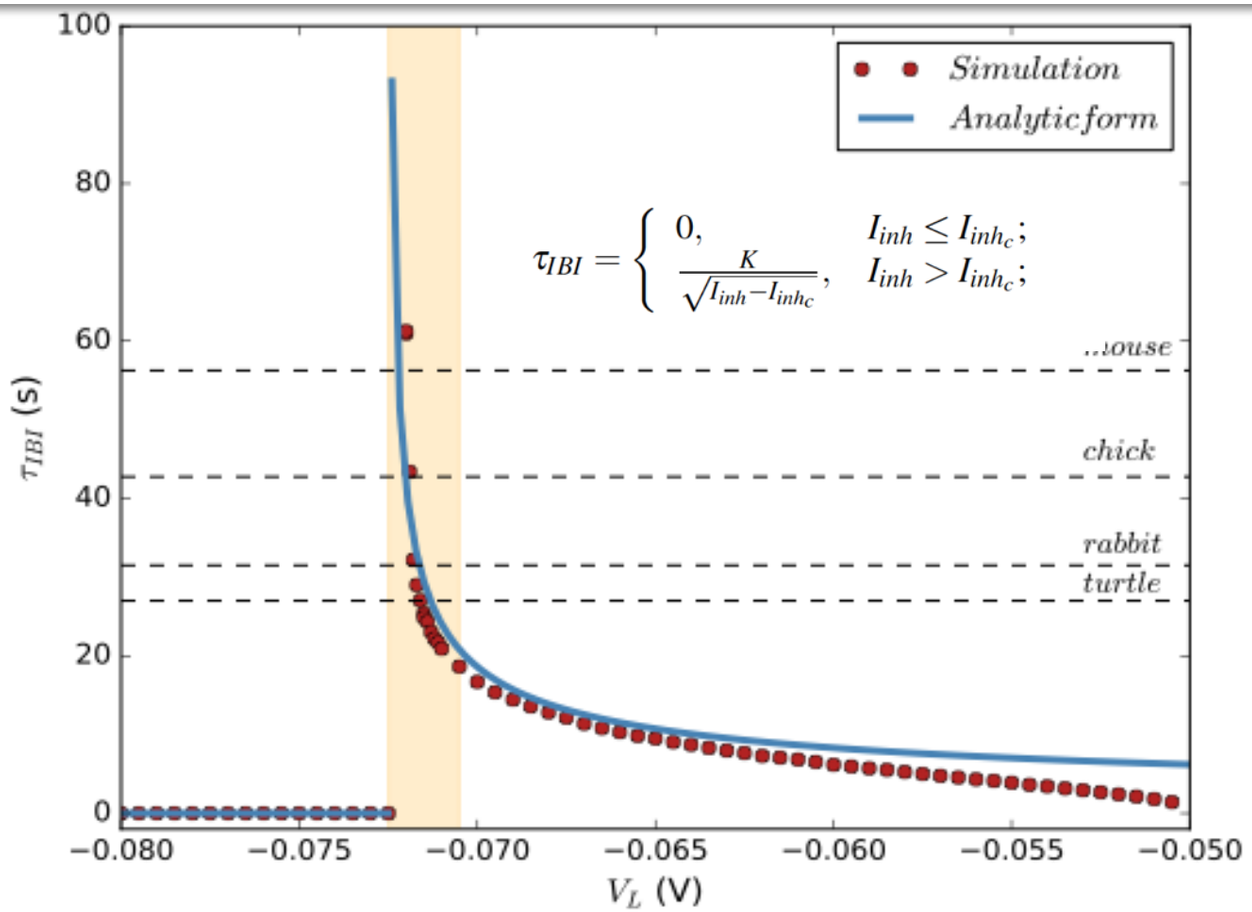
Variability within retinal waves

i) Across species

Godfrey et al. 2007

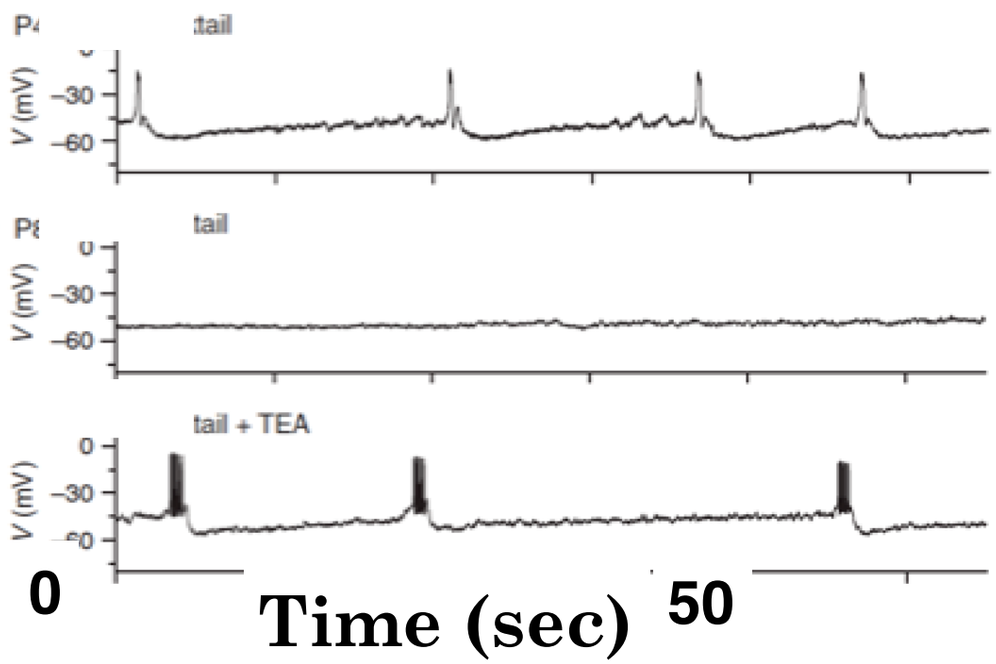


Interburst intervals



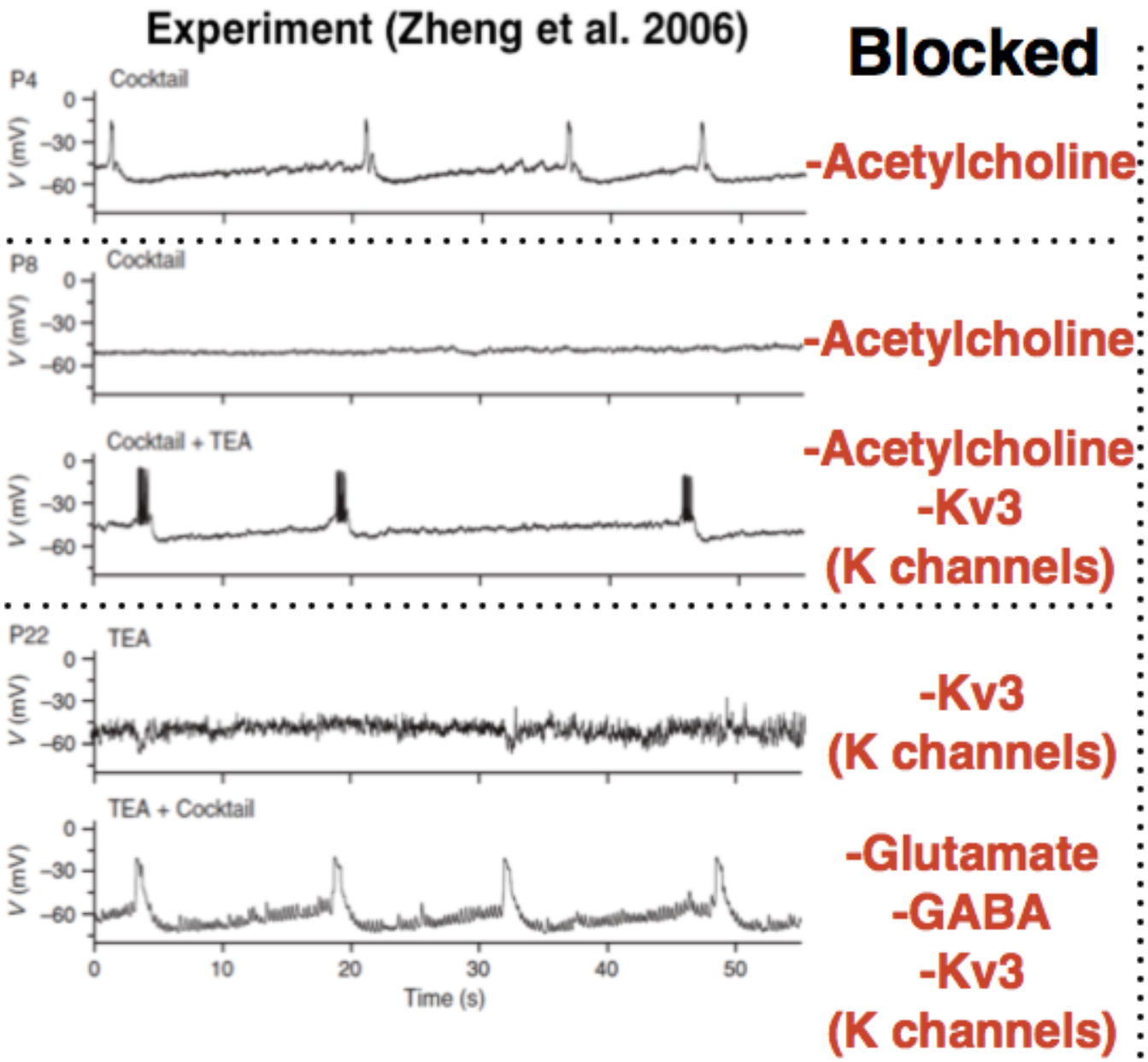
Variability within retinal waves

iii) Pharmacology



How do SACs lose their excitability?

A



Blocked

-Acetylcholine

-Acetylcholine

-Acetylcholine
-Kv3
(K channels)

-Kv3
(K channels)

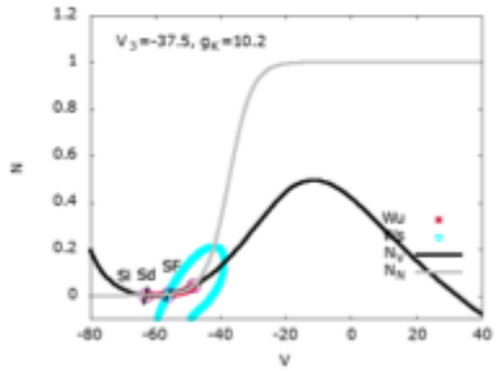
-Glutamate
-GABA
-Kv3
(K channels)

Potassium channels (potentially Kv3) are modelled by 3 parameters

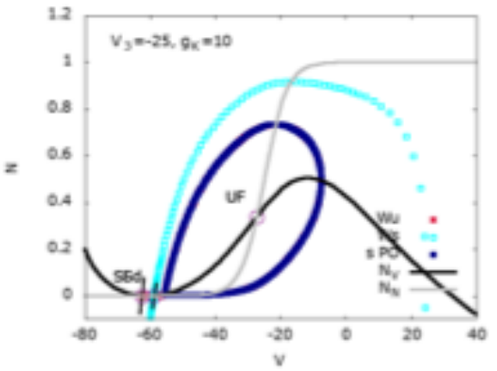
gK, V3, V4

*TEA blocks Kv3 channels

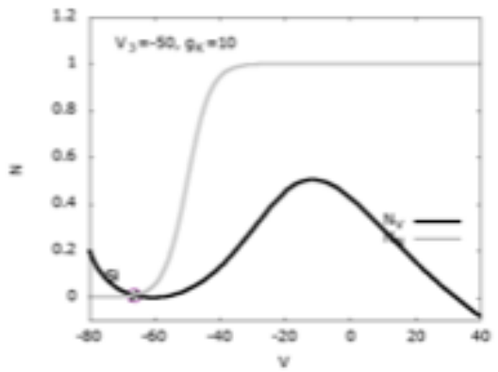
B

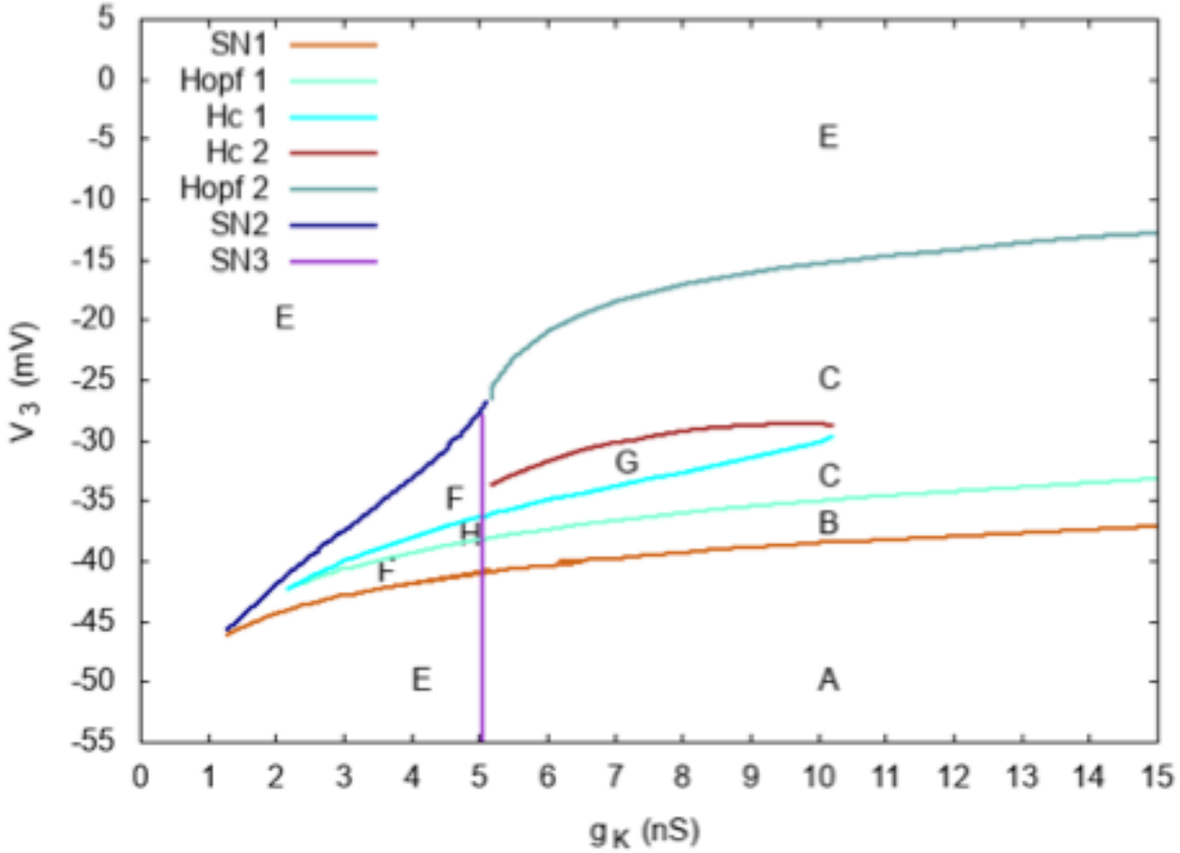

V3=-37.5, gK=10.2
Si Sd
SF
Wu
Ws
NV
NN
N
V

C

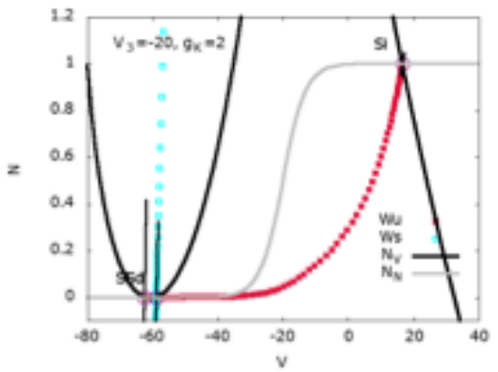

V3=-25, gK=10
UF
SFd
Wu
Ws
s PO
NV
NN
N
V

A

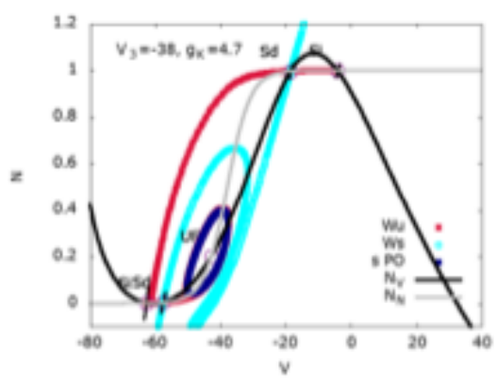

V3=-50, gK=10
Sl
NV
N
V


SN1
Hopf 1
Hc 1
Hc 2
Hopf 2
SN2
SN3
E
C
G
F
H
F'
B
E
A
V3 (mV)
gK (nS)

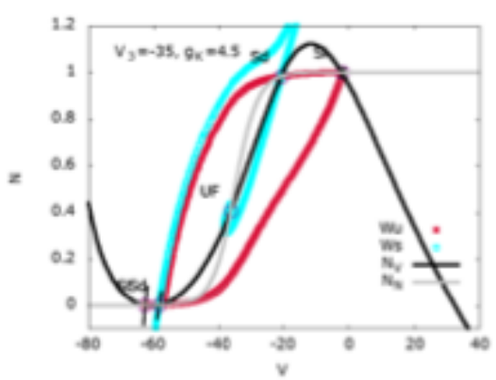
E


V3=-20, gK=2
Si
SFd
Wu
Ws
NV
NN
N
V

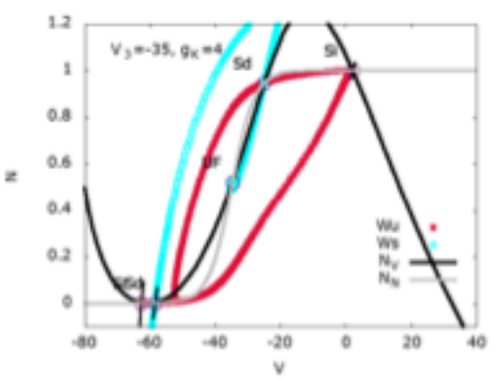
H


V3=-38, gK=4.7
Sd
Sl
UF
SFd
Wu
Ws
s PO
NV
NN
N
V

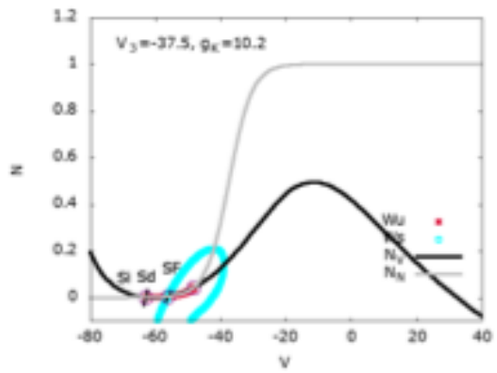
G


V3=-35, gK=4.5
Sd
Sl
UF
SFd
Wu
Ws
NV
NN
N
V

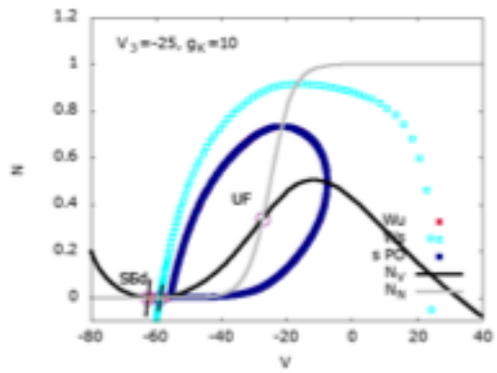
F


V3=-35, gK=4
Sd
Sl
SF
SFd
Wu
Ws
NV
NN
N
V

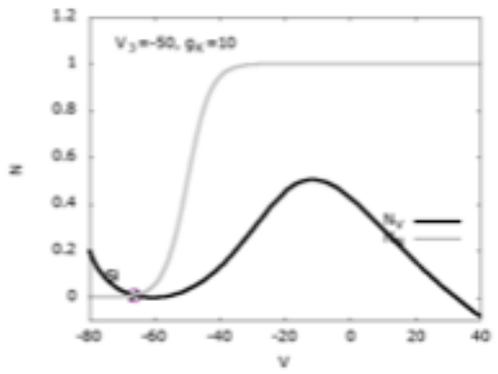
B

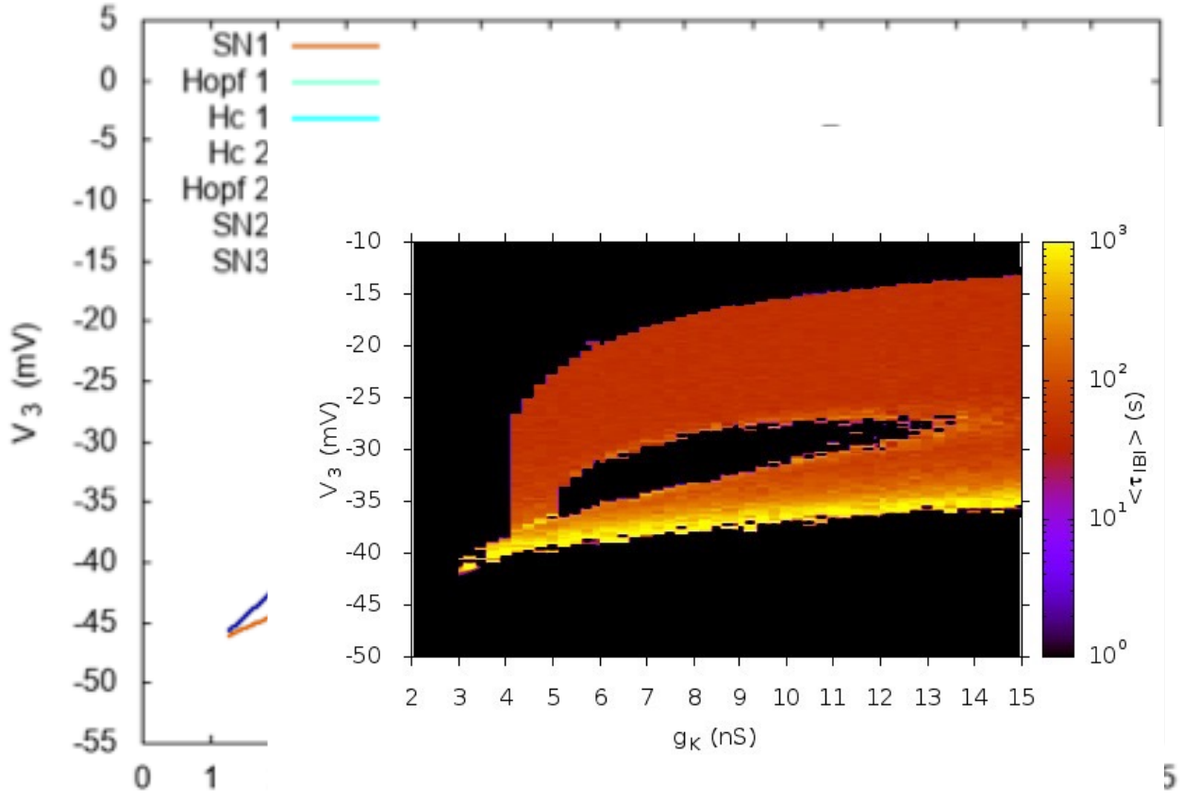

V3=-37.5, gK=10.2
Si Sd
SF
Wu
Ws
NV
NN
N
V

C

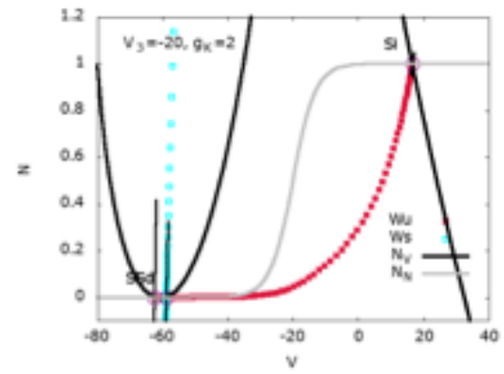

V3=-25, gK=10
UF
SFd
Wu
Ws
s PO
NV
NN
N
V

A

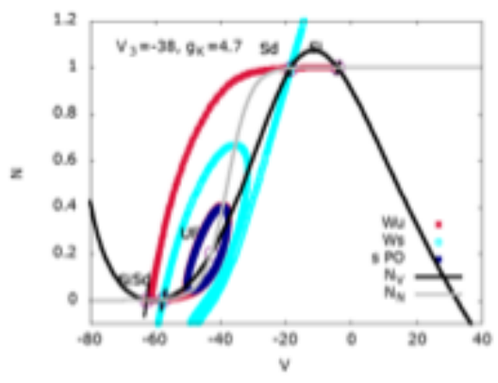

V3=-50, gK=10
Si
NV
N
V


SN1
Hopf 1
Hc 1
Hc 2
Hopf 2
SN2
SN3
V3 (mV)
gK (nS)
<τIBI> (s)

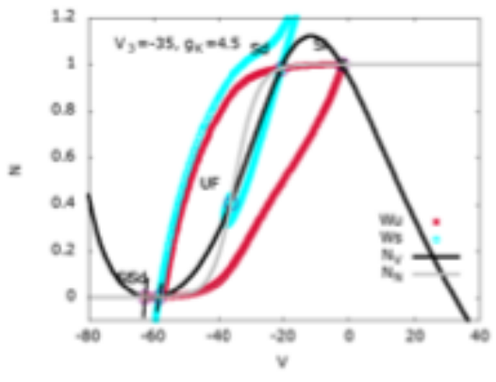
E


V3=-20, gK=2
Si
SFd
Wu
Ws
NV
NN
N
V

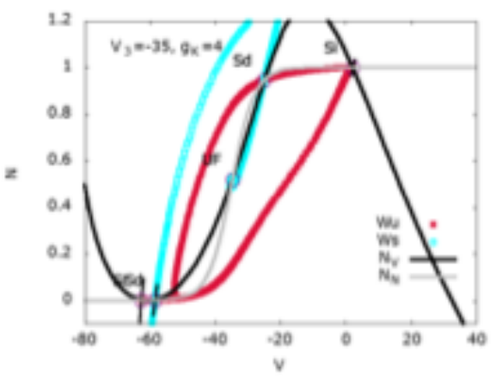
H


V3=-38, gK=4.7
Sd
Si
UF
SFd
Wu
Ws
s PO
NV
NN
N
V

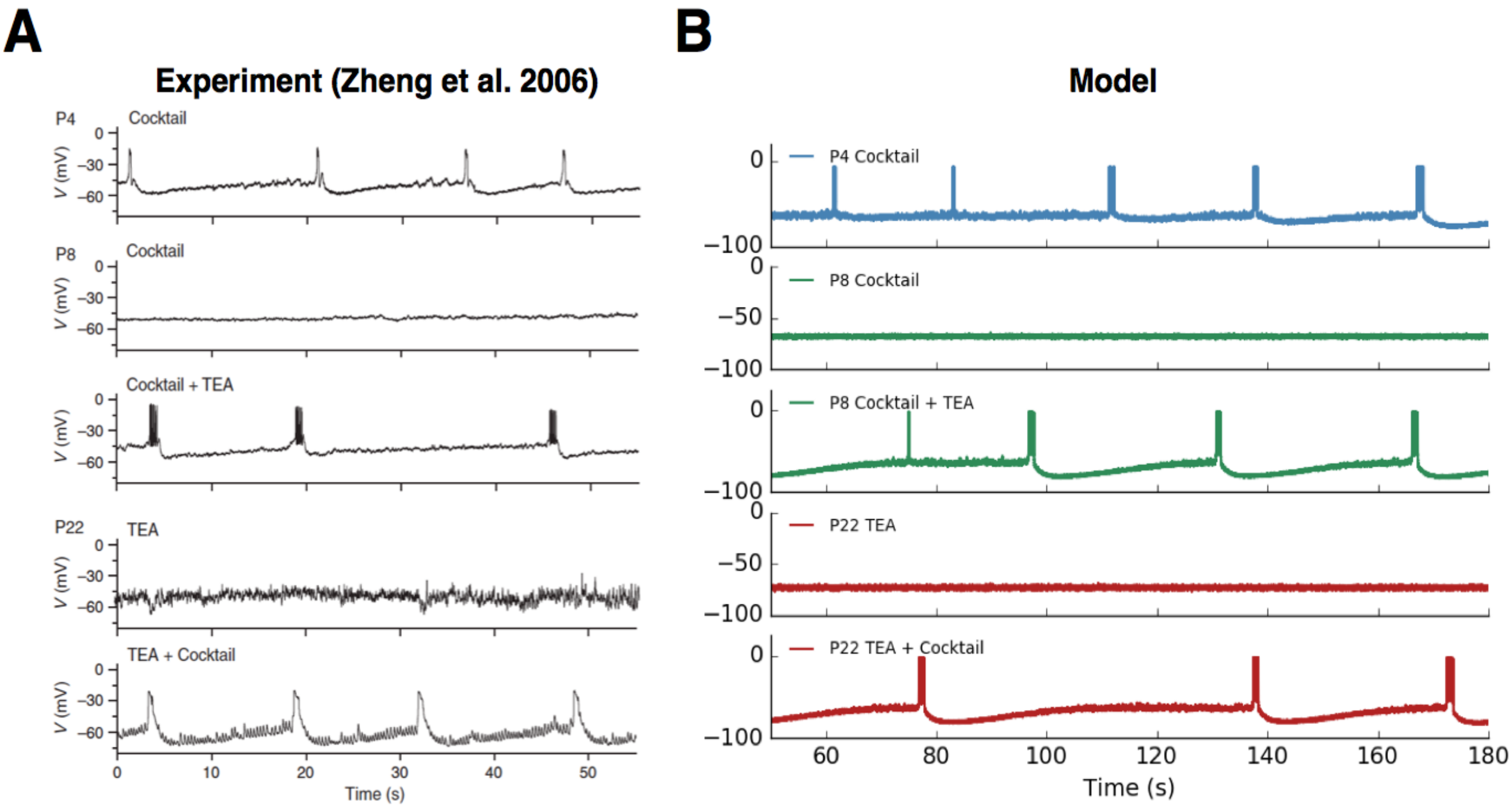
G


V3=-35, gK=4.5
Sd
Si
UF
SFd
Wu
Ws
NV
NN
N
V

F


V3=-35, gK=4
Sd
Si
SF
SFd
Wu
Ws
NV
NN
N
V

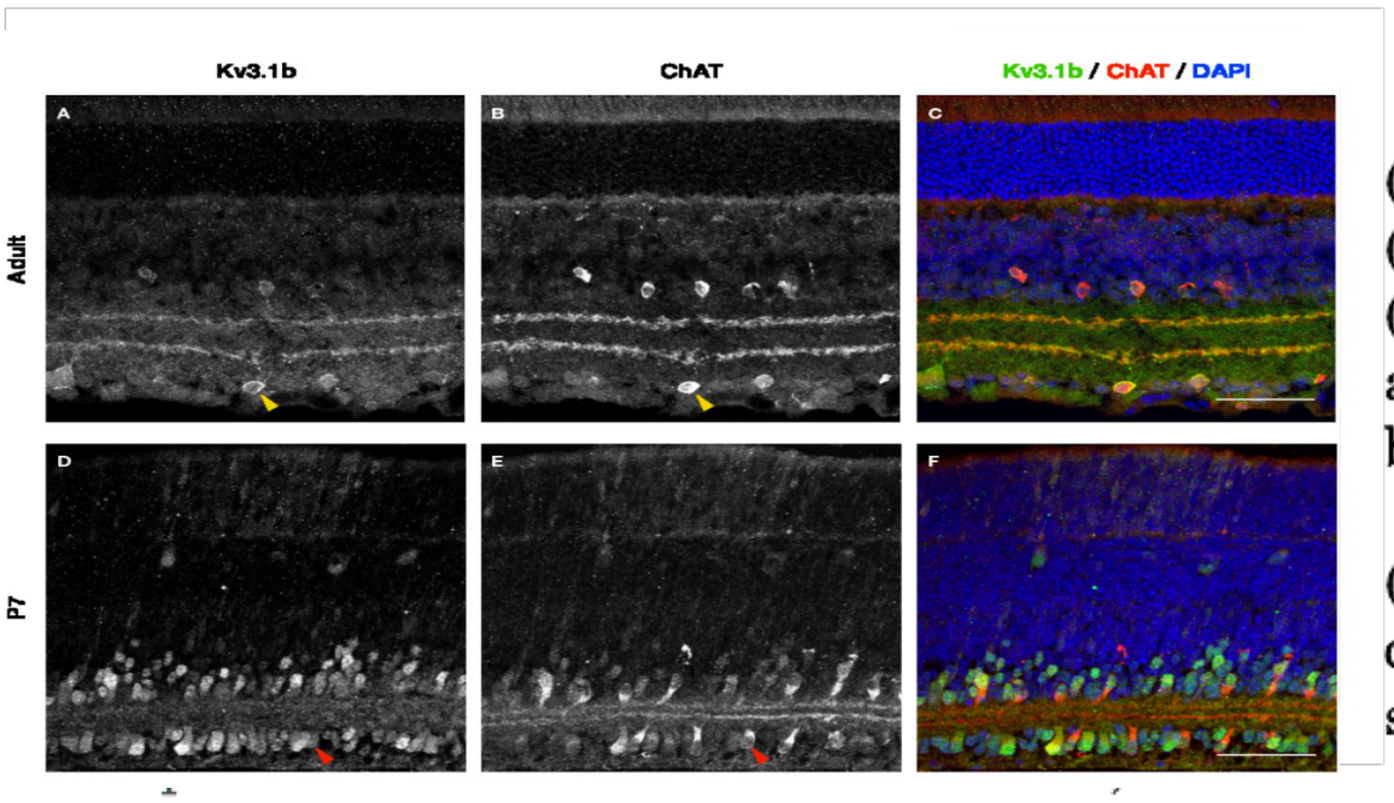
Predict the role of Kv3 channels in the loss of SACs excitability



How do SACs lose their excitability?

Hypothesis: The expression of the potassium Kv3 channels increases upon maturation possibly leading to the loss of SACs excitability

Preliminary experimental exploration



(O.Marre-E. Orendorff)

Localization of Kv3.1b in adult and P7 retinas.

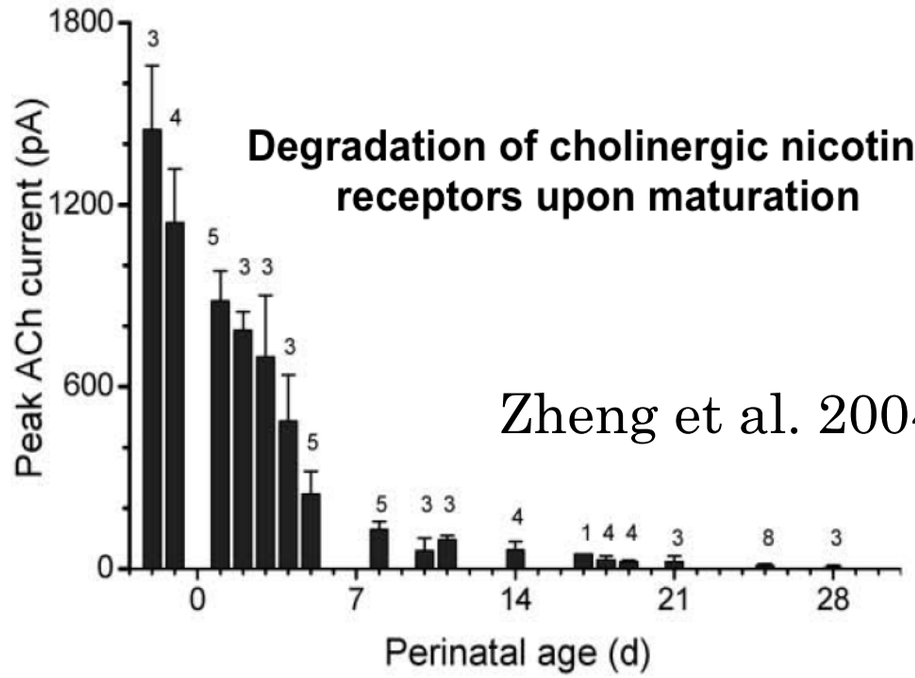
(A-C) Adult retina section showing Kv3.1b (green) and choline acetyltransferase (ChAT, red) reactivity in starburst amacrine cells. Cell nuclei stain (DAPI, blue).

(D-F) P7 retina section showing little colocalization of Kv3.1b with ChAT in starburst amacrine cells.

However, results are preliminary as experiment is not yet conclusive

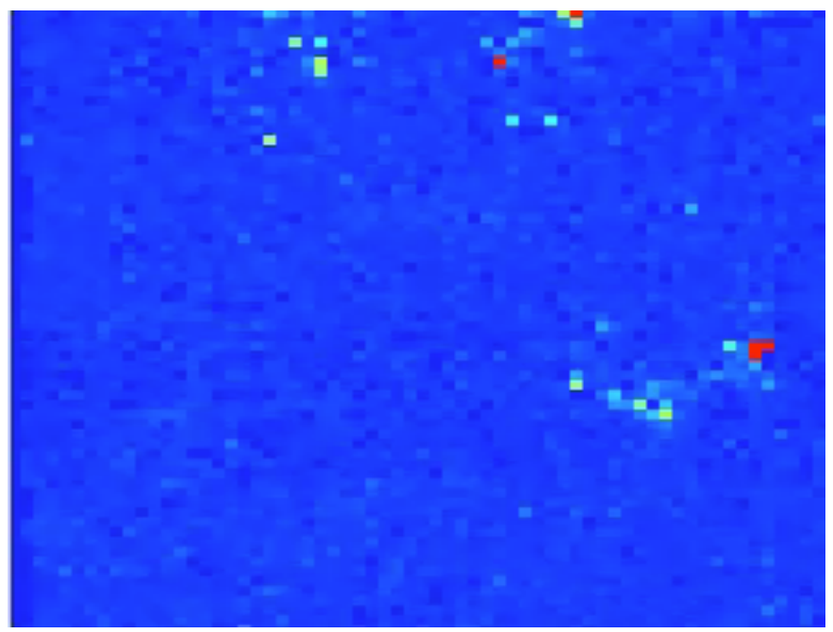
Variability <u>within</u> retinal waves

ii) Development



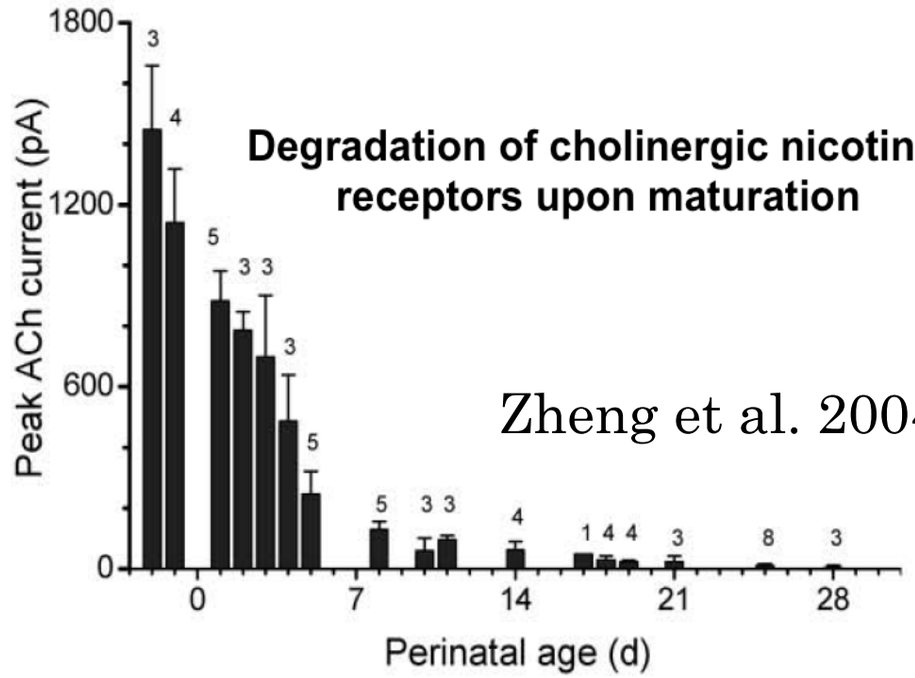
Zheng et al. 2004

iv) Spatial Variability



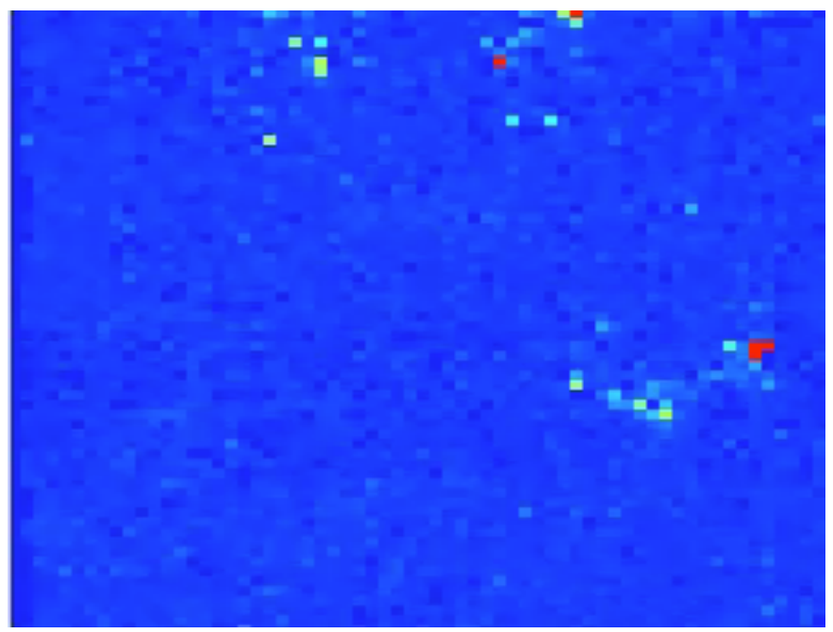
Variability <u>within</u> retinal waves

ii) Development



Zheng et al. 2004

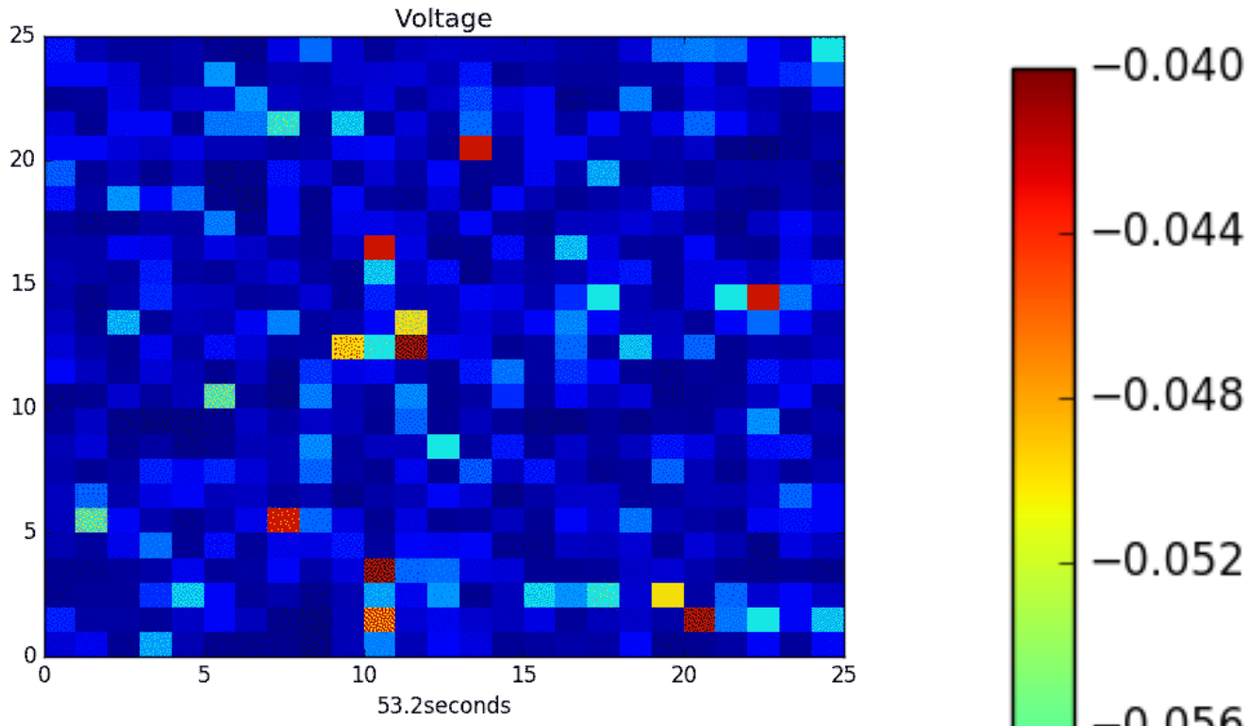
iv) Spatial Variability



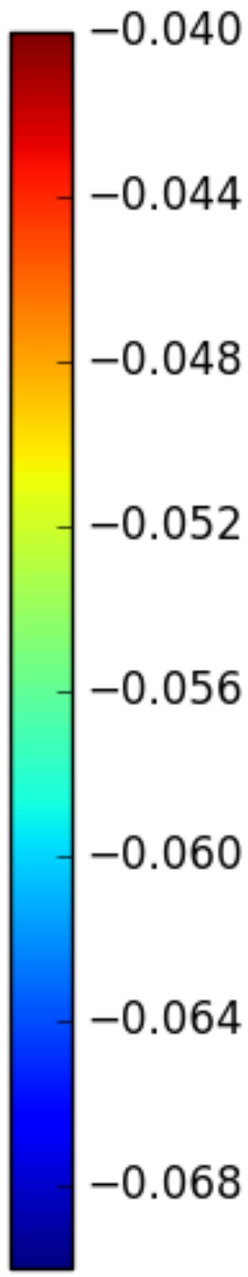
Network of SACs : Simulated Voltage

Isolated Neurons

gach=0.126 nS



gach=0.168 nS

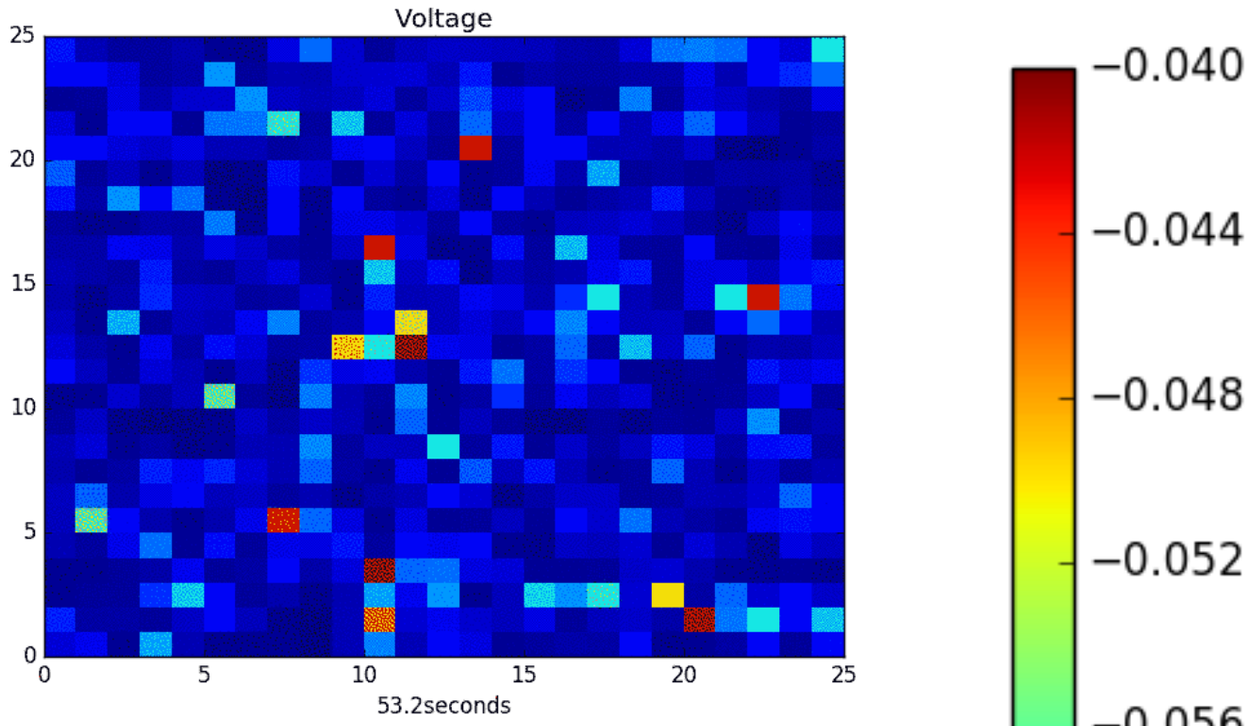


gach=0.21 nS

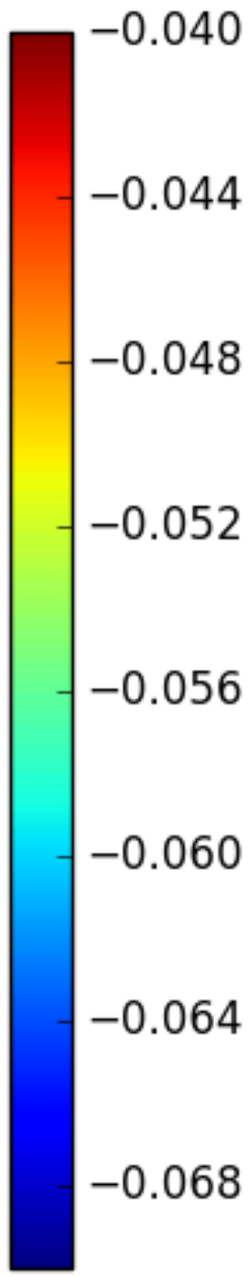
Network of SACs : Simulated Voltage

Isolated Neurons

gach=0.126 nS



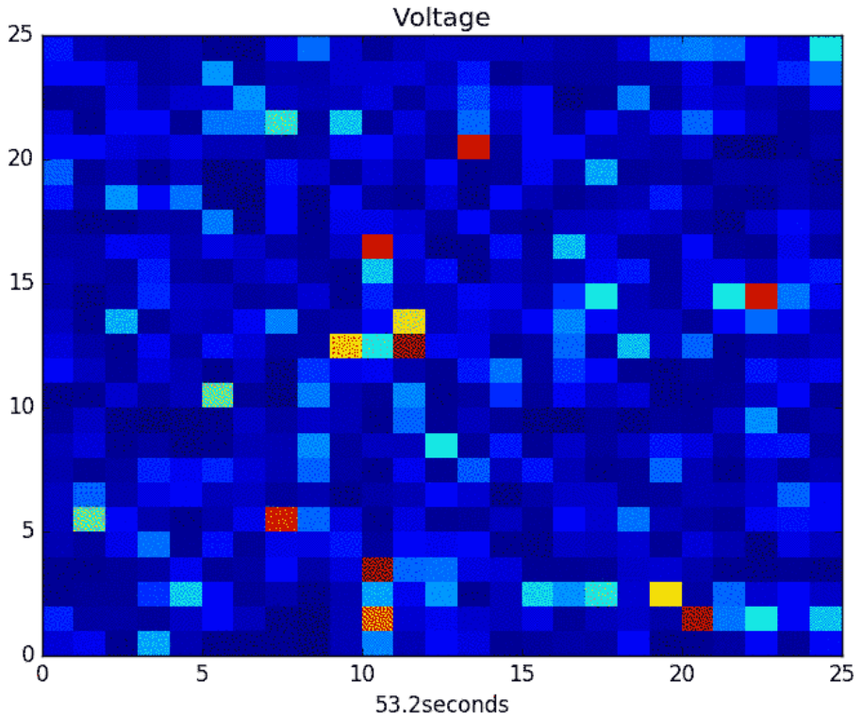
gach=0.168 nS



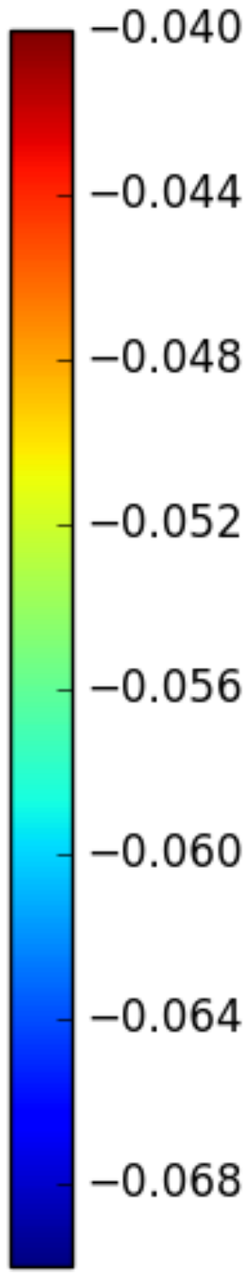
gach=0.21 nS

Network of SACs : Simulated Voltage

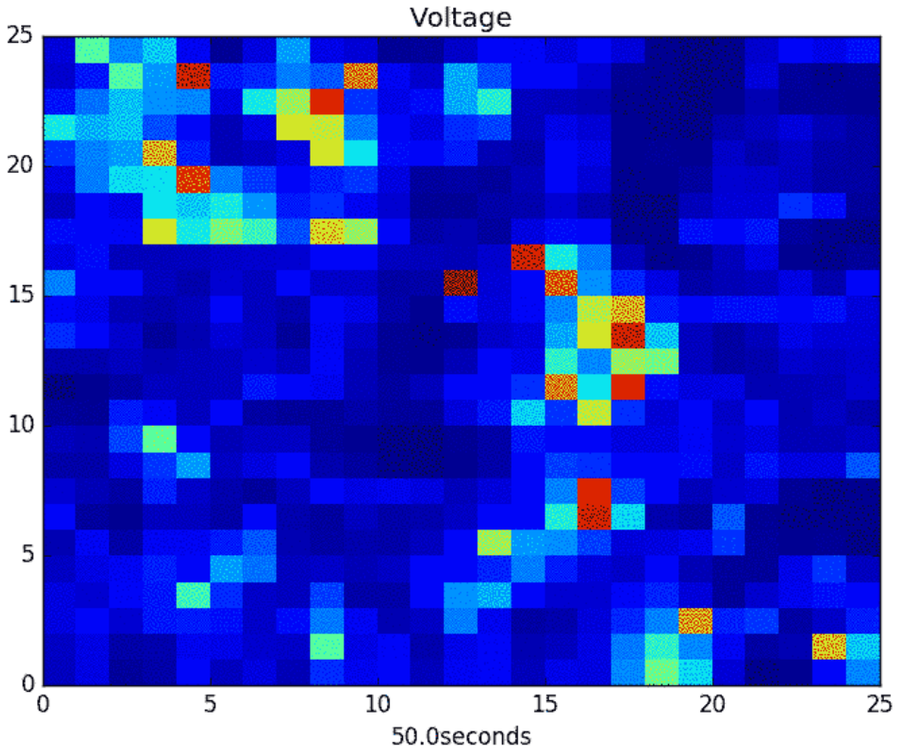
Isolated Neurons



gach=0.168 nS



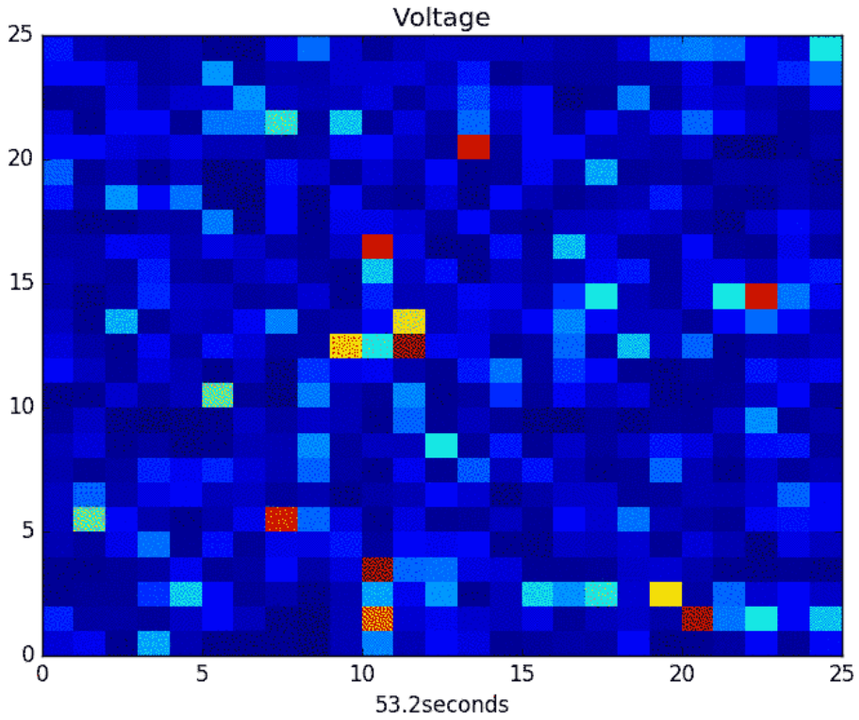
gach=0.126 nS



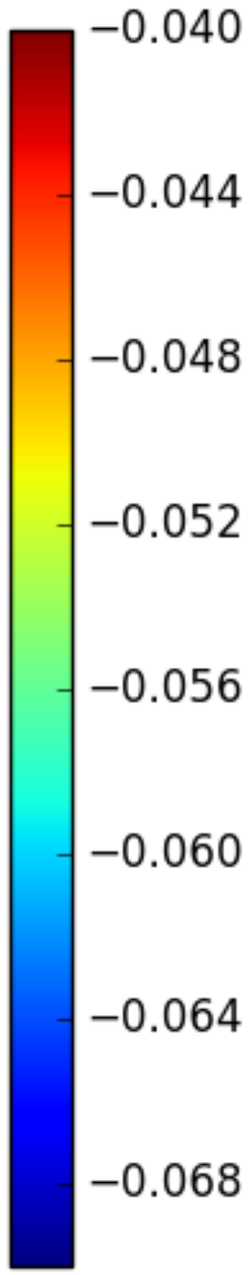
gach=0.21 nS

Network of SACs : Simulated Voltage

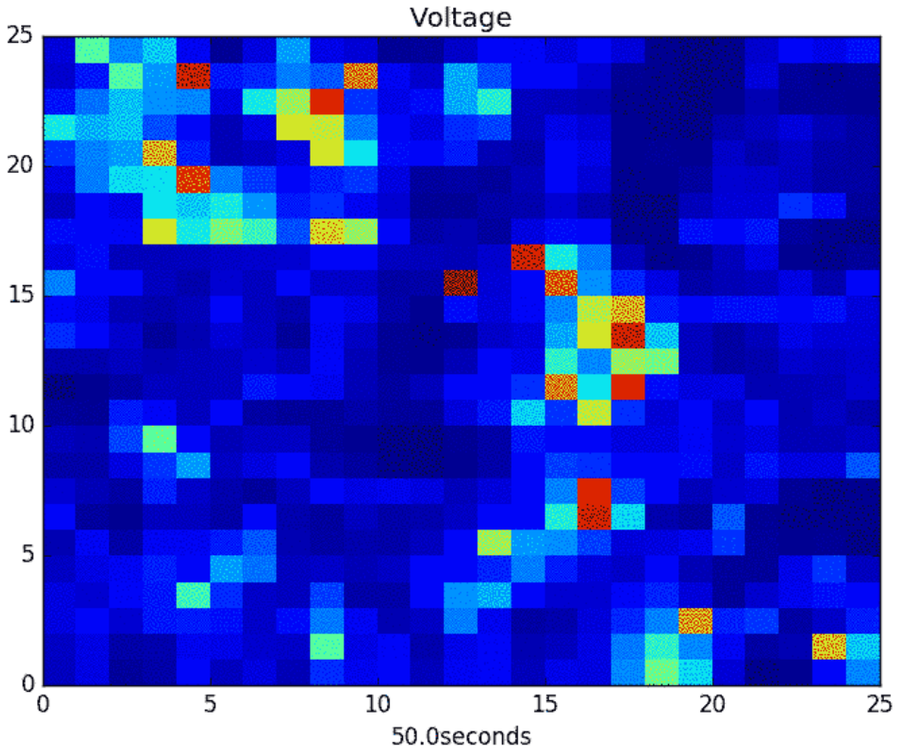
Isolated Neurons



gach=0.168 nS



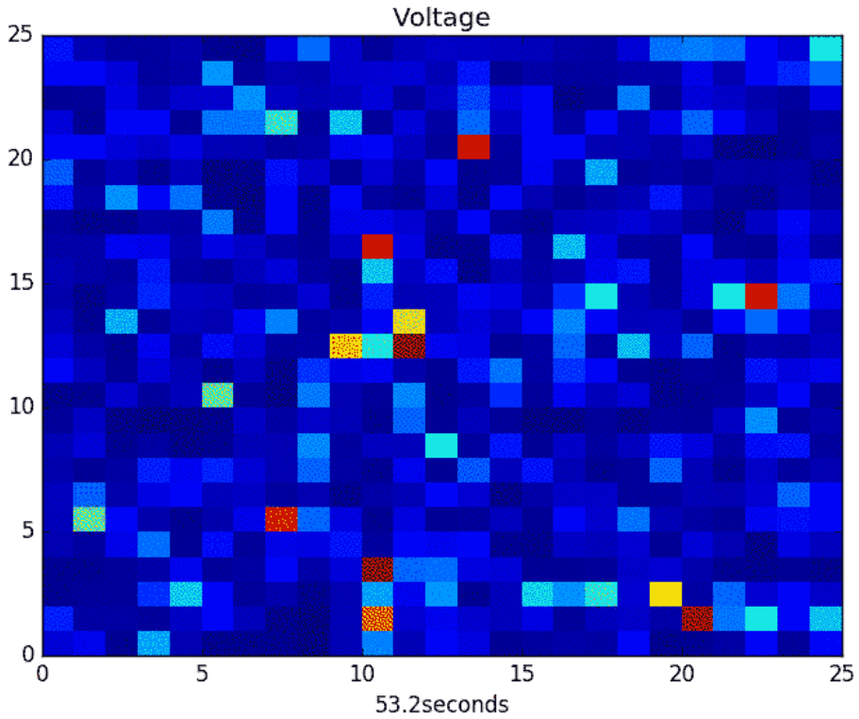
gach=0.126 nS



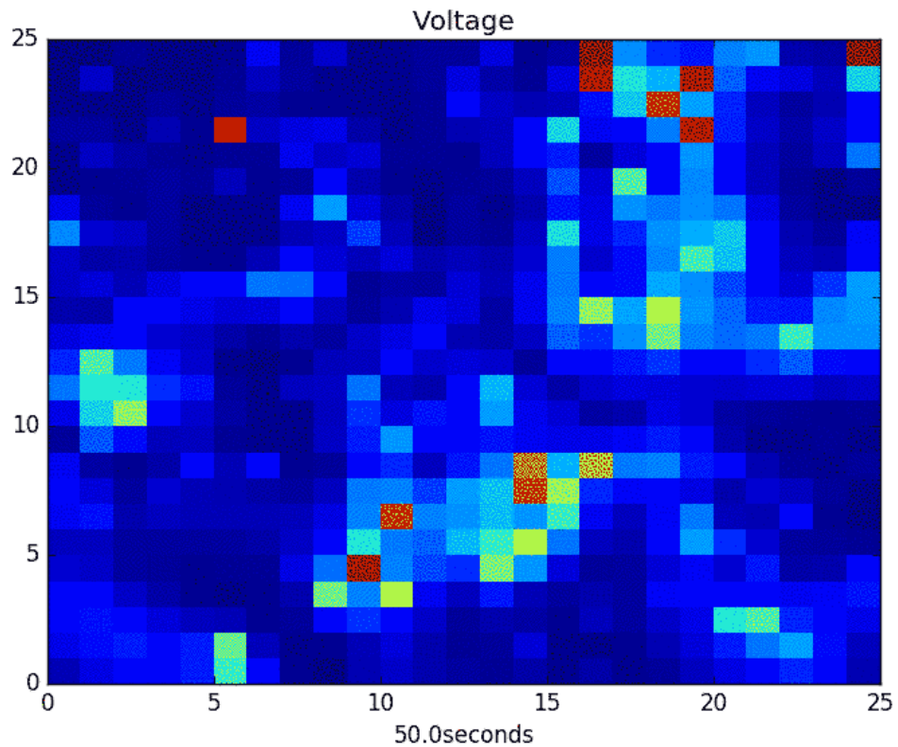
gach=0.21 nS

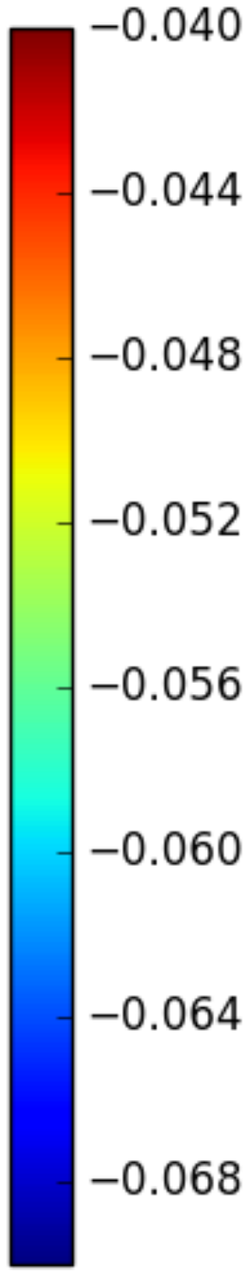
Network of SACs : Simulated Voltage

Isolated Neurons

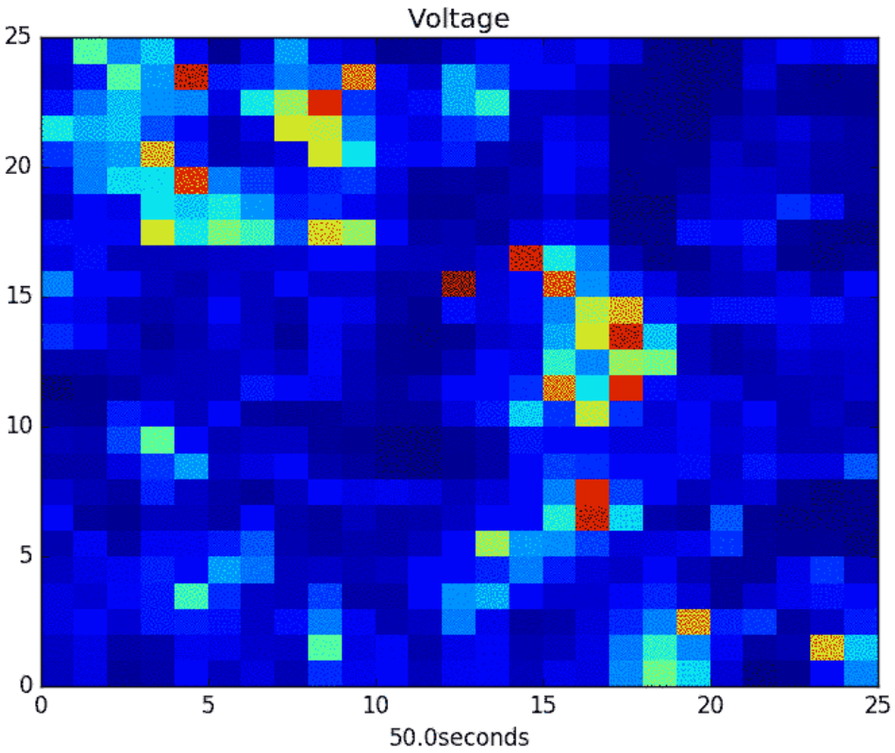


gach=0.168 nS





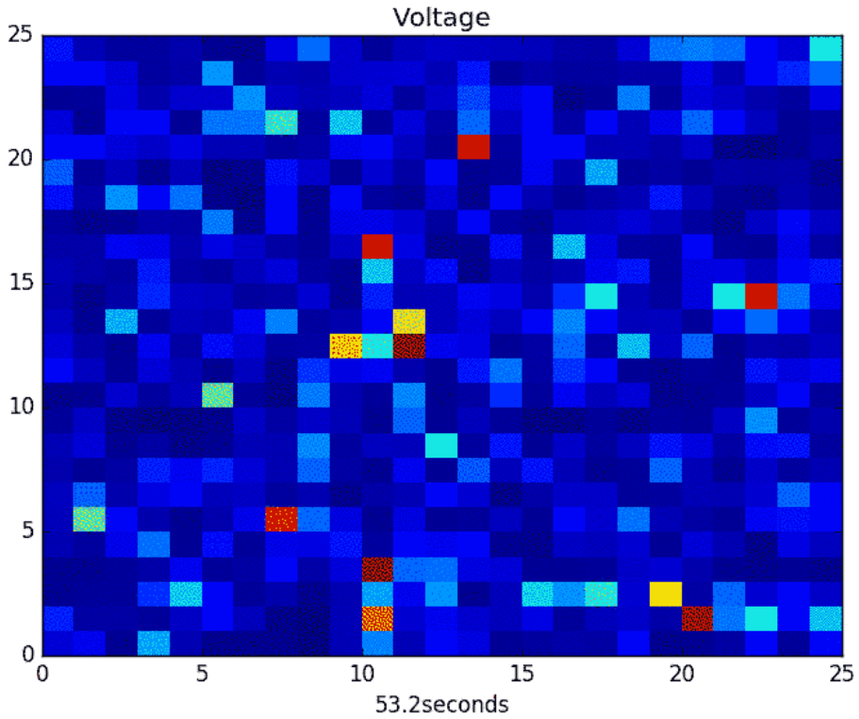
gach=0.126 nS



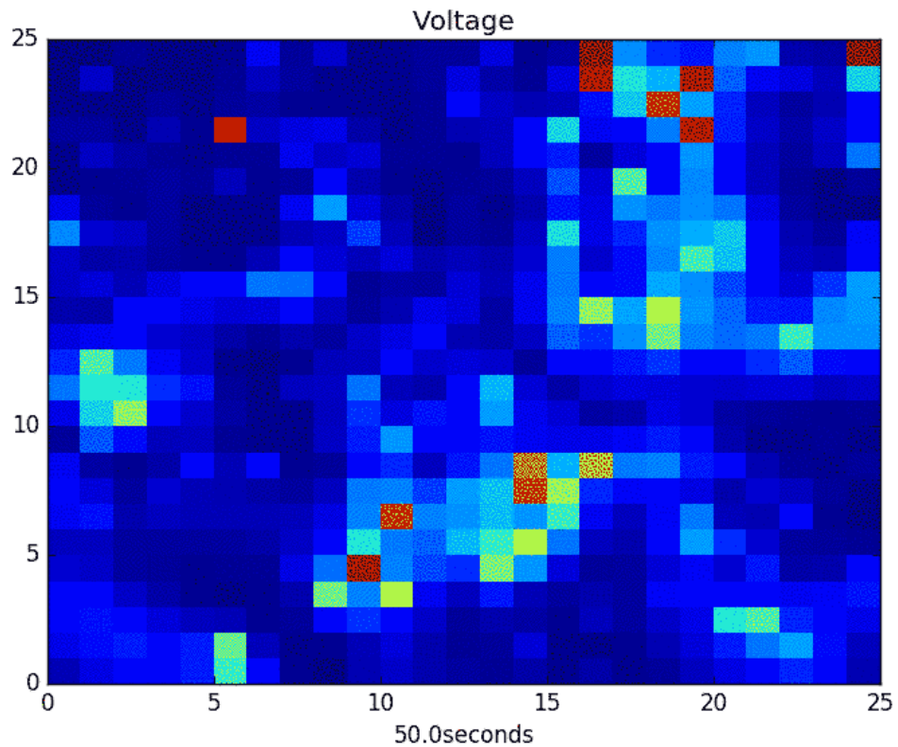
gach=0.21 nS

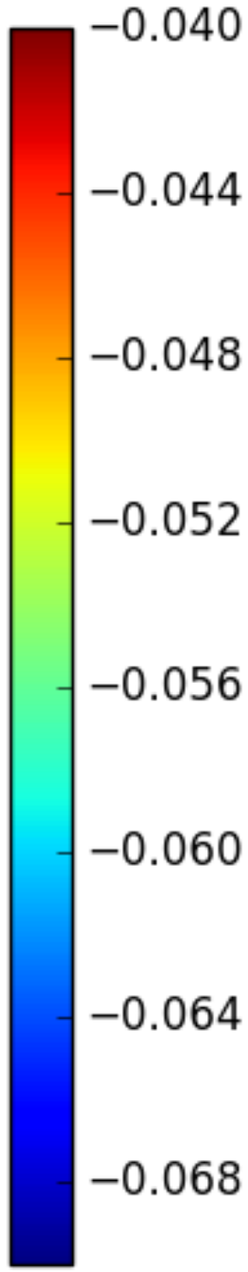
Network of SACs : Simulated Voltage

Isolated Neurons

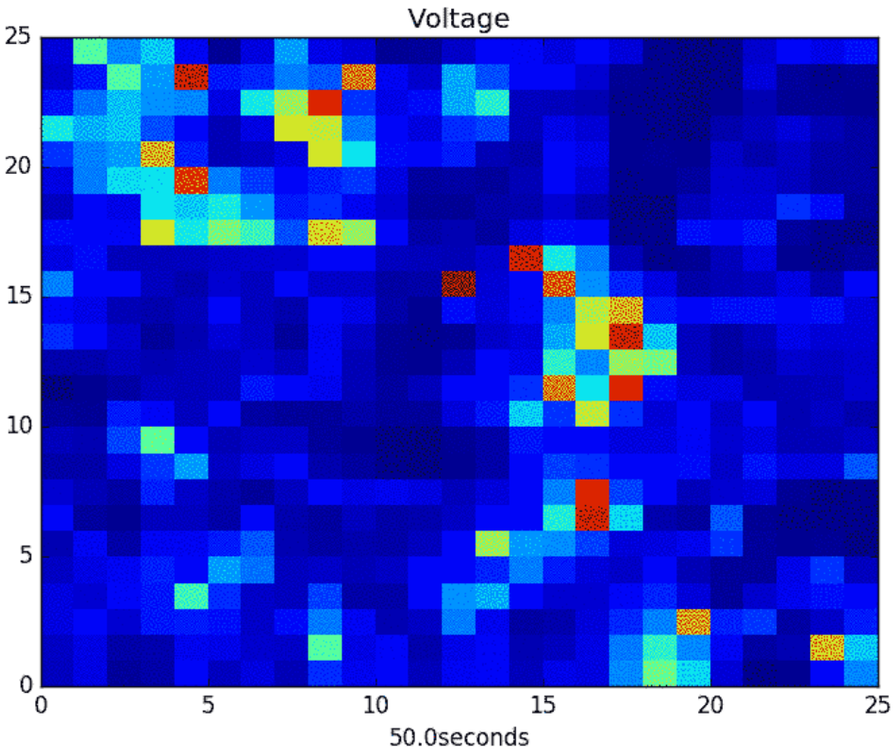


gach=0.168 nS





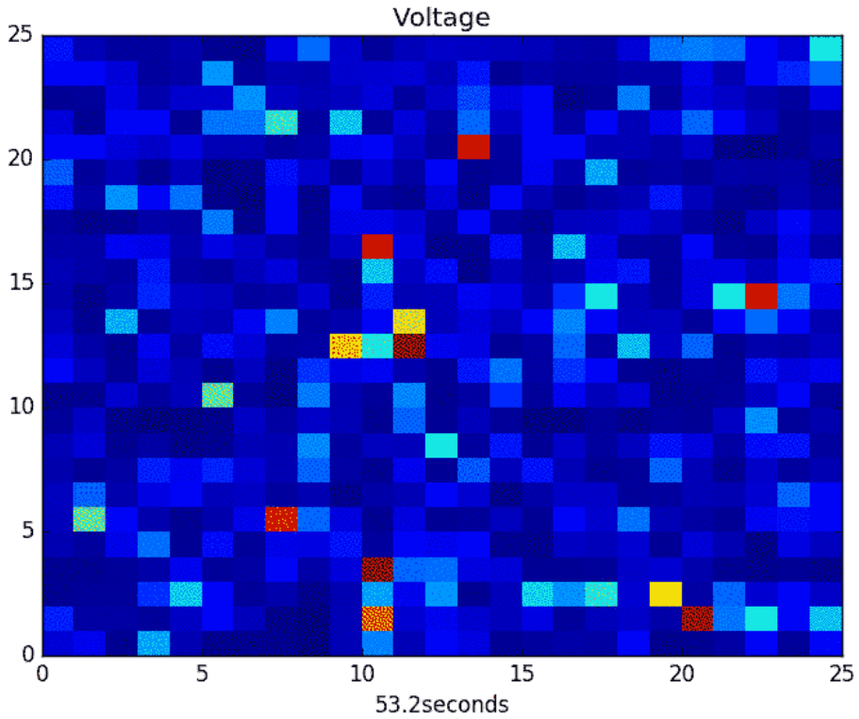
gach=0.126 nS



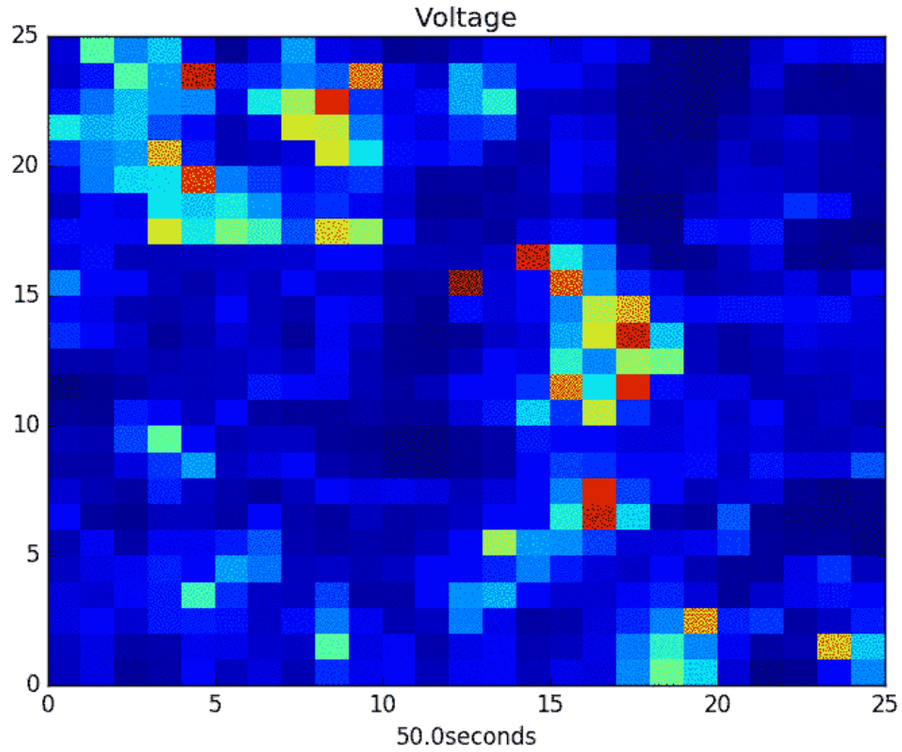
gach=0.21 nS

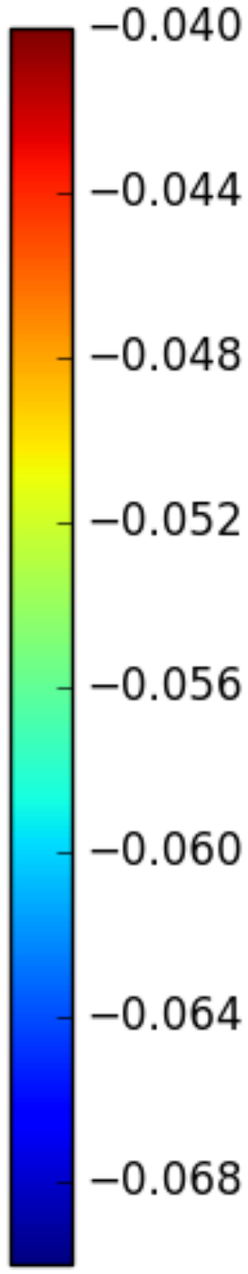
Network of SACs : Simulated Voltage

Isolated Neurons

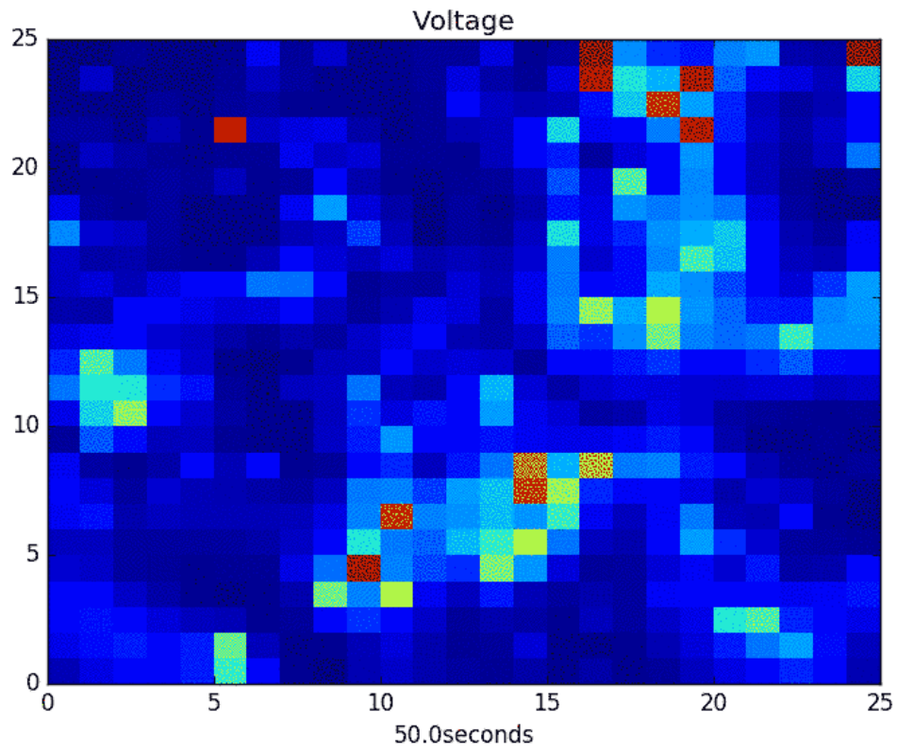


gach=0.126 nS

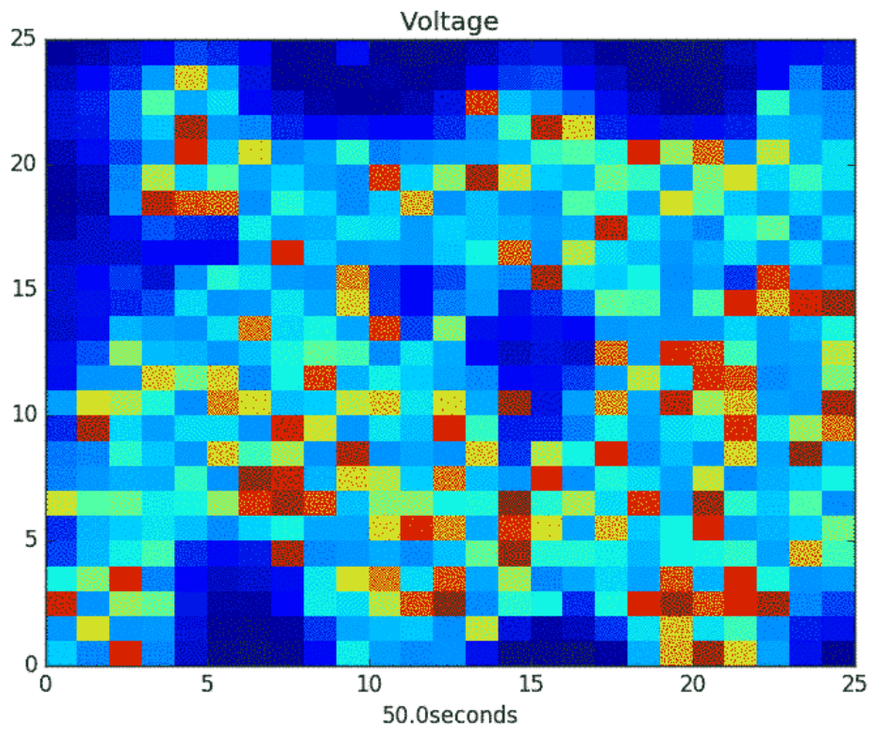




gach=0.168 nS

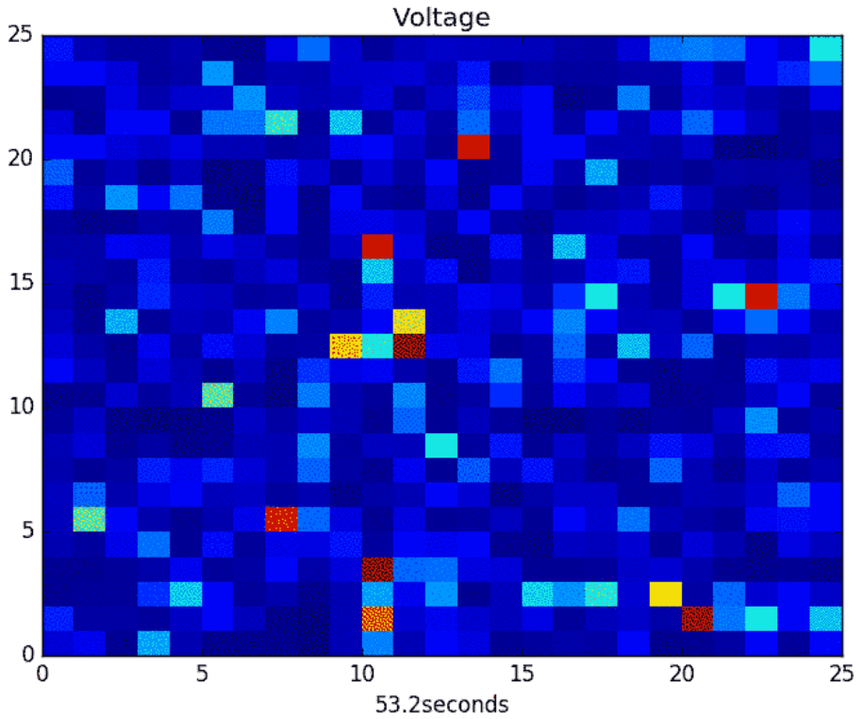


gach=0.21 nS

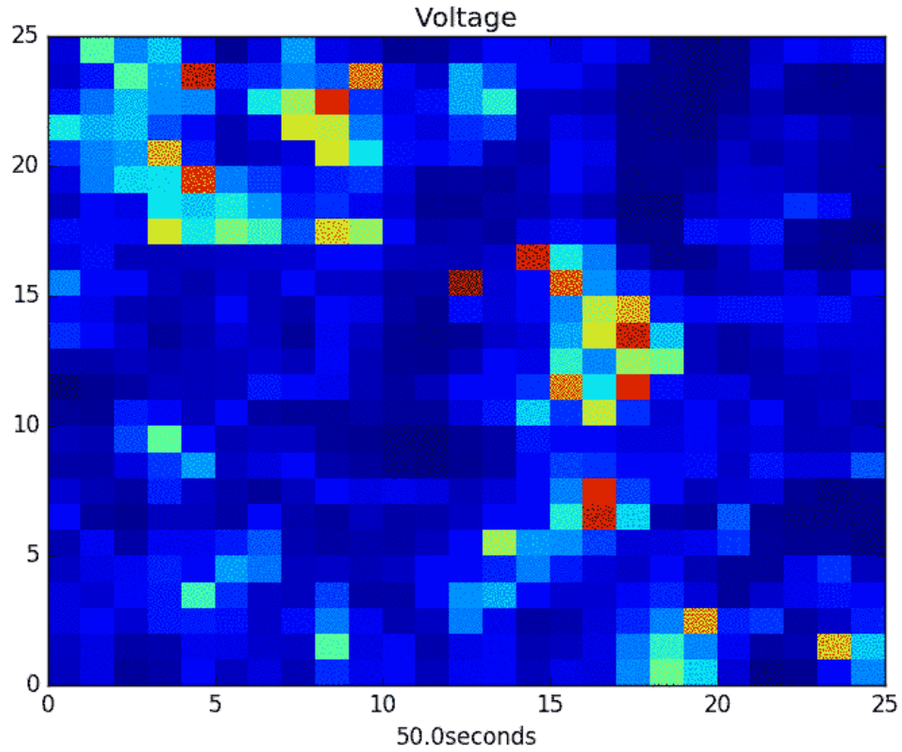


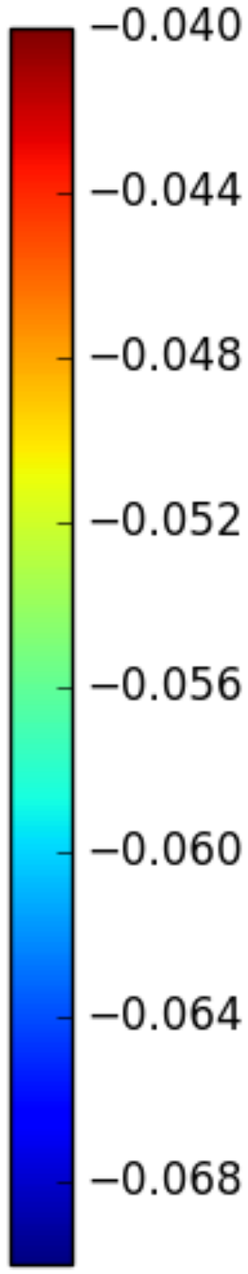
Network of SACs : Simulated Voltage

Isolated Neurons

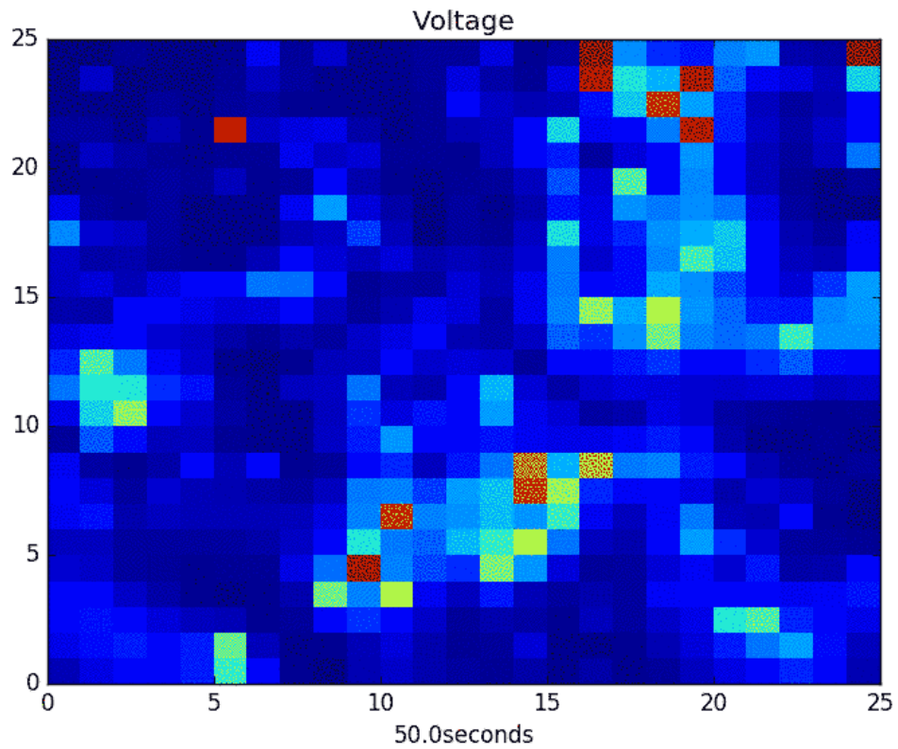


gach=0.126 nS

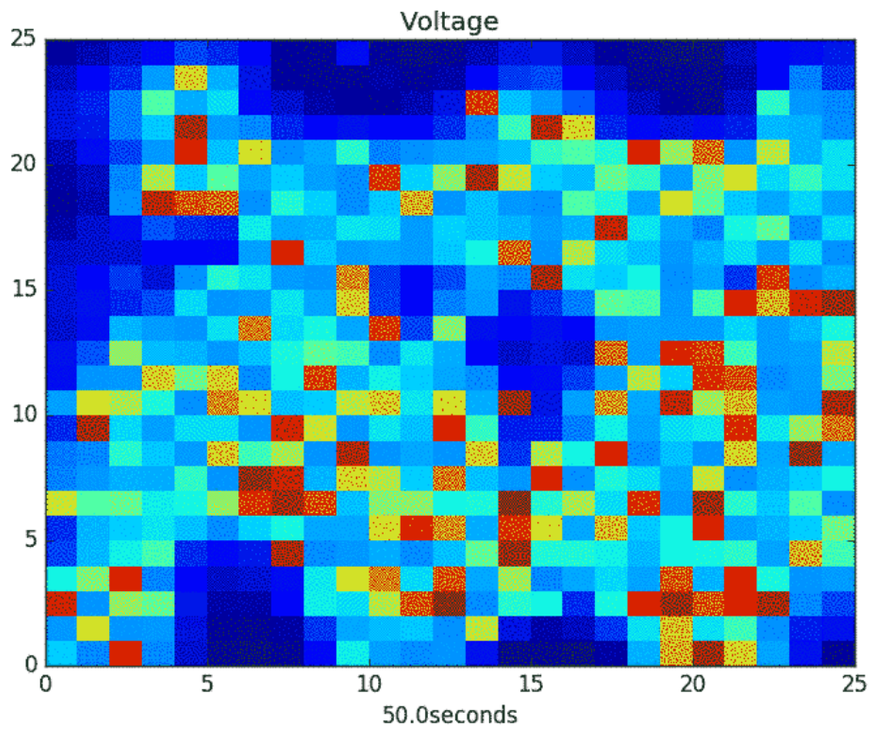




gach=0.168 nS

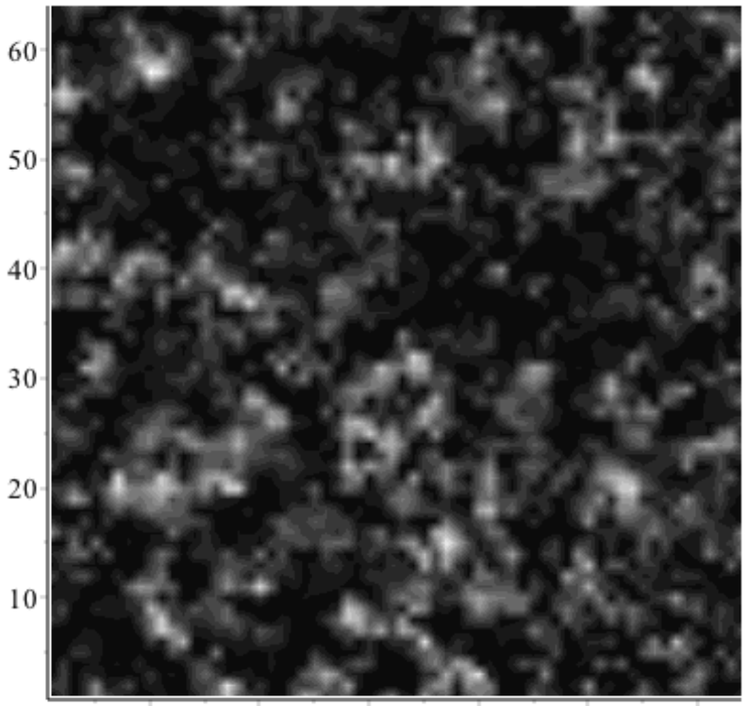


gach=0.21 nS

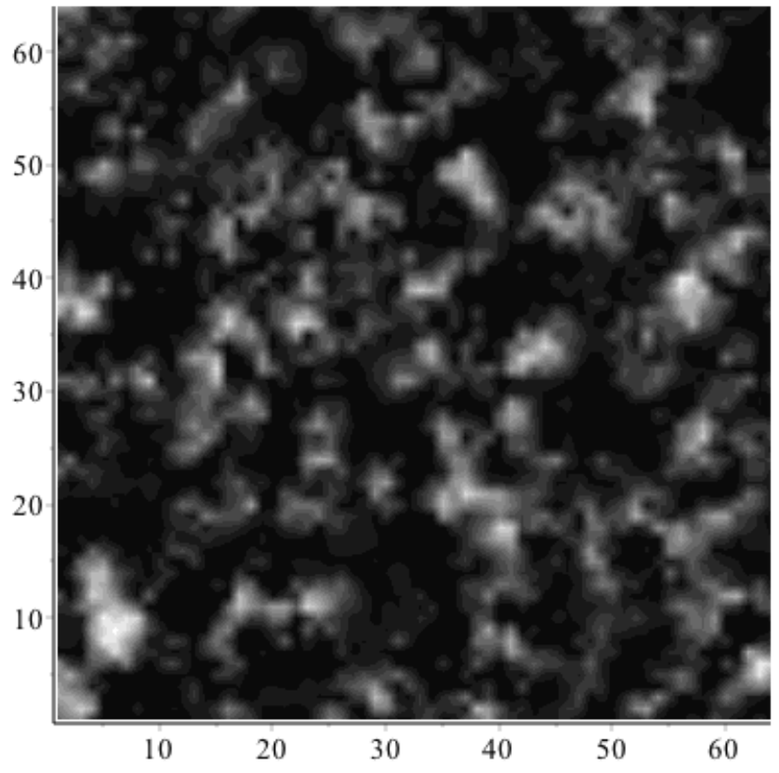


Network of SACs : Simulated Calcium Concentration

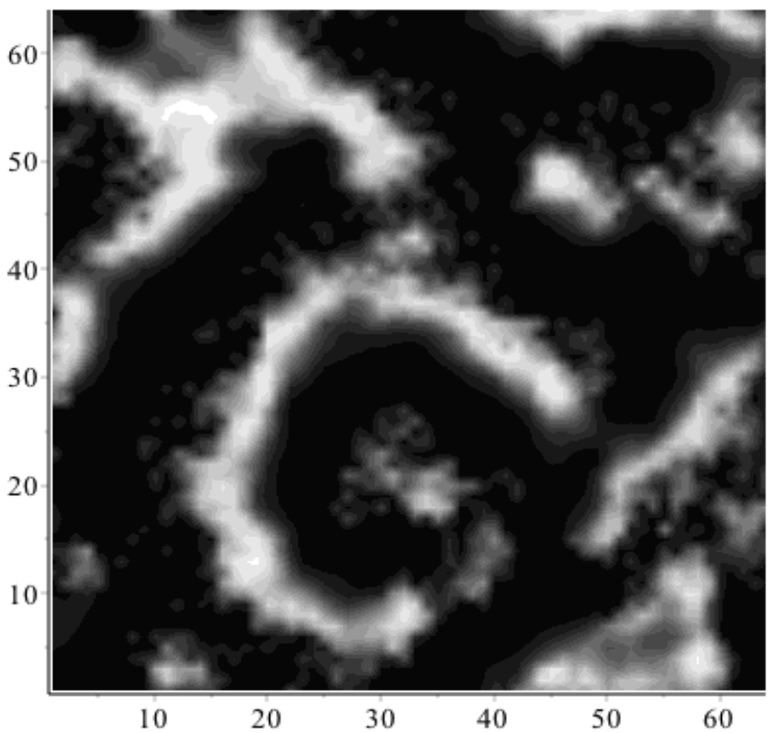
gach=0.102 nS



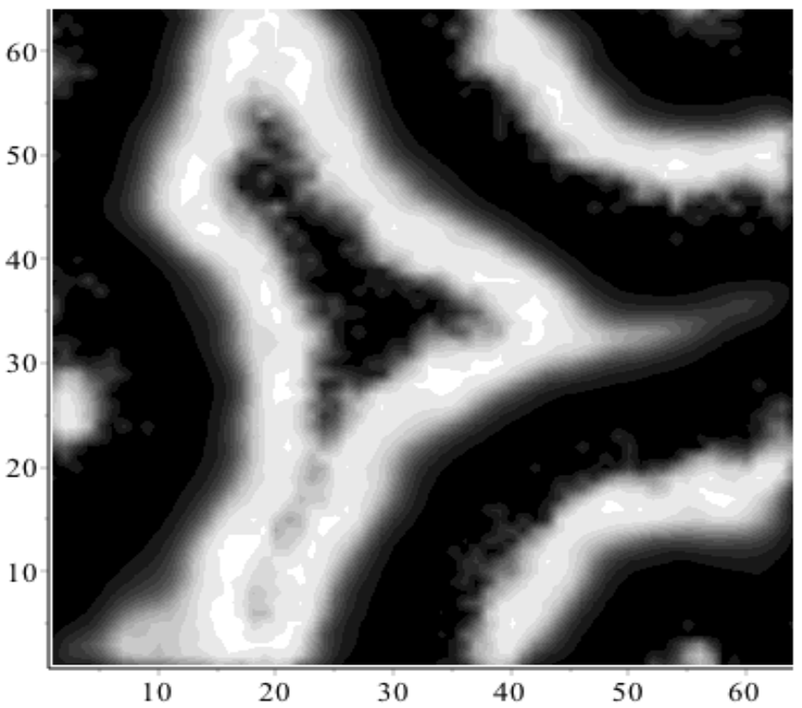
gach=0.126 nS



gach=0.168 nS

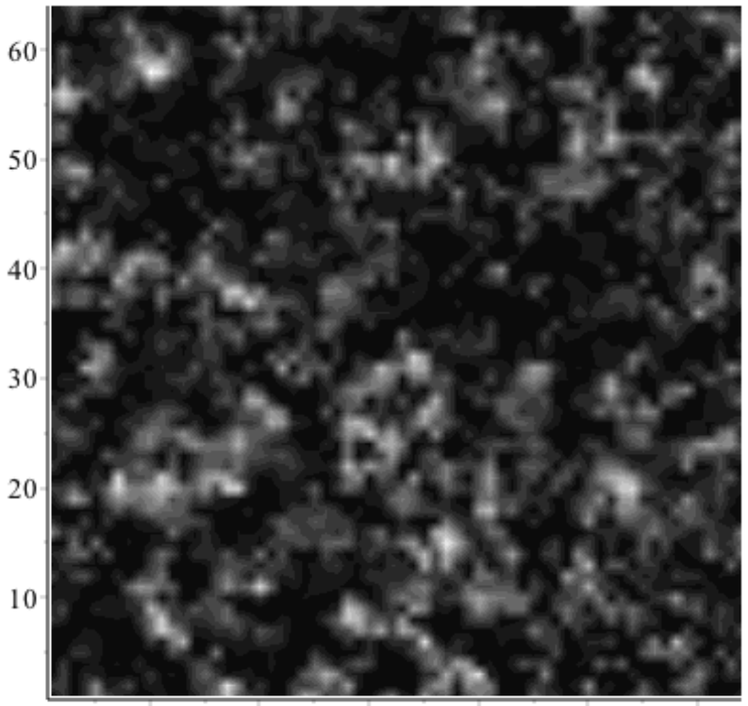


gach=0.21 nS

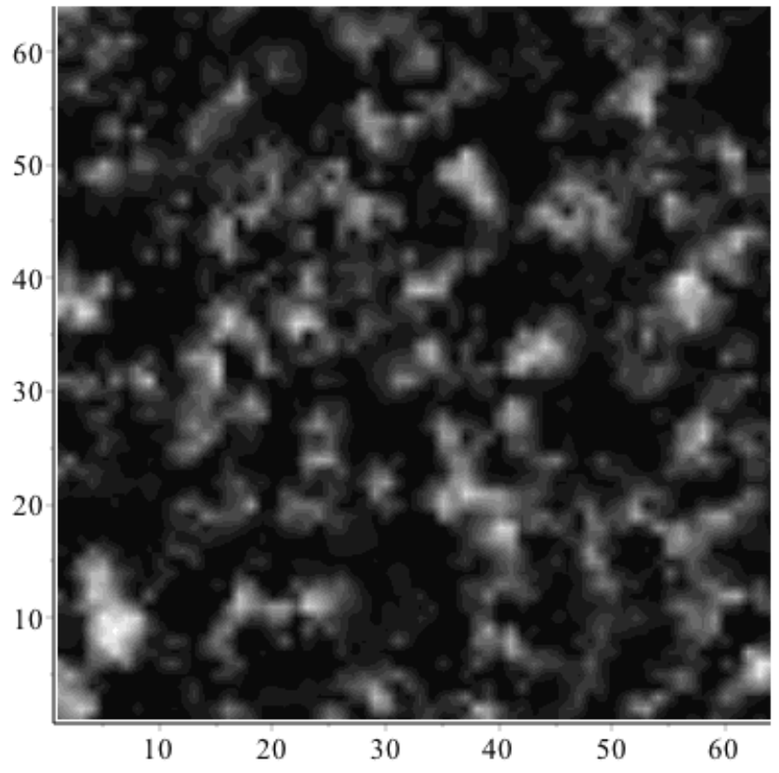


Network of SACs : Simulated Calcium Concentration

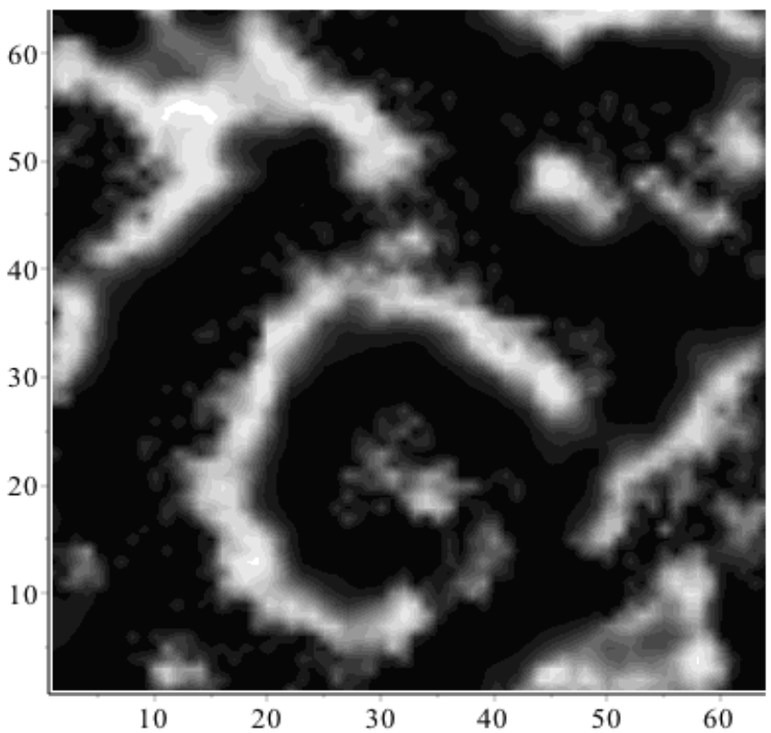
gach=0.102 nS



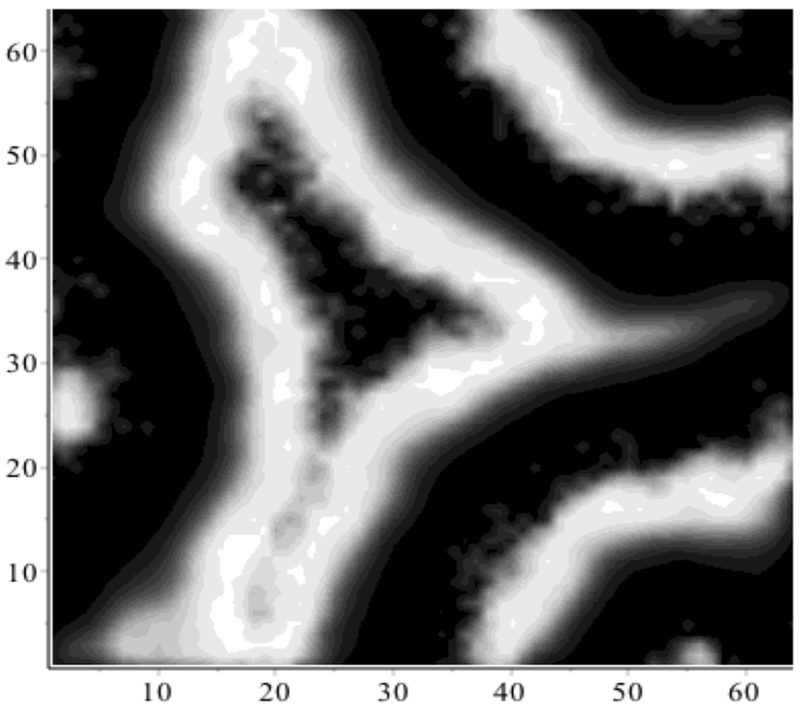
gach=0.126 nS



gach=0.168 nS

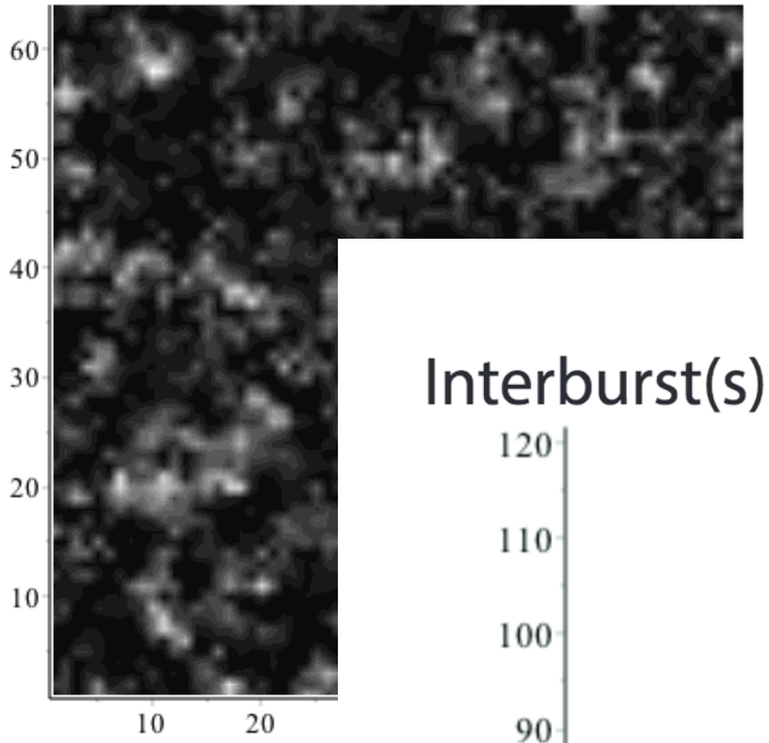


gach=0.21 nS

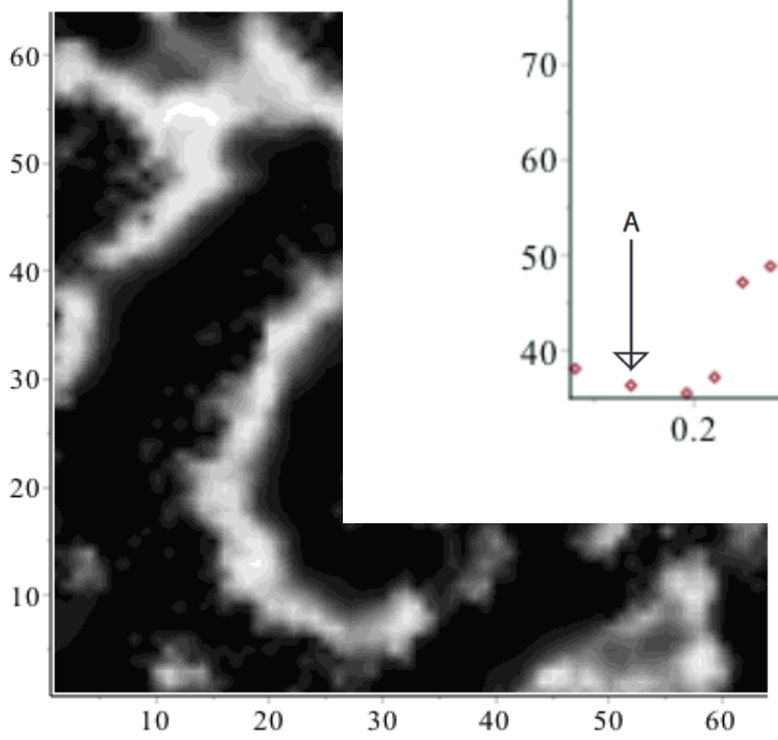


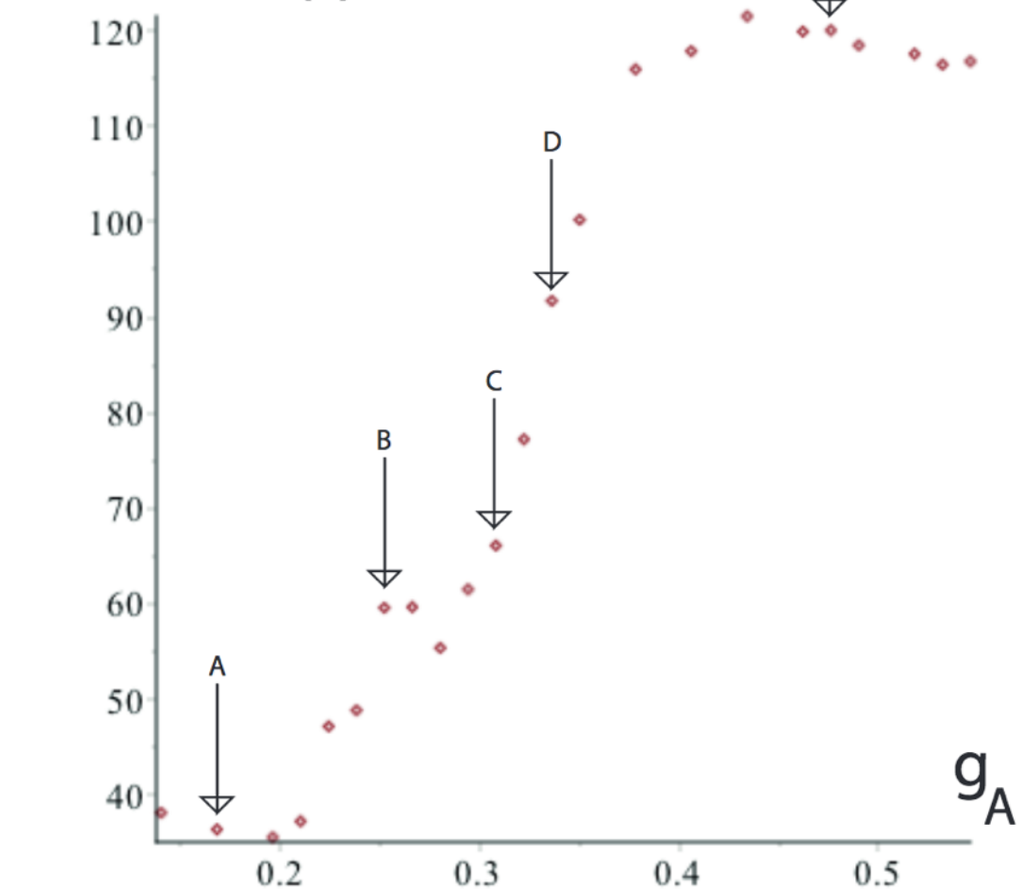
Network of SACs : Simulated Calcium Concentration

gach=0.102 nS

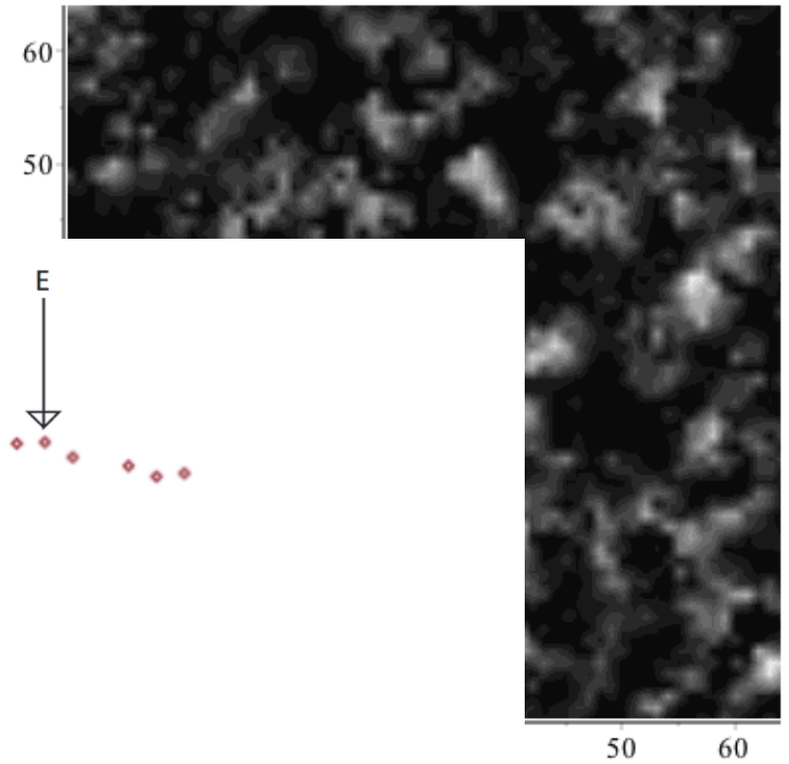


gach=0.

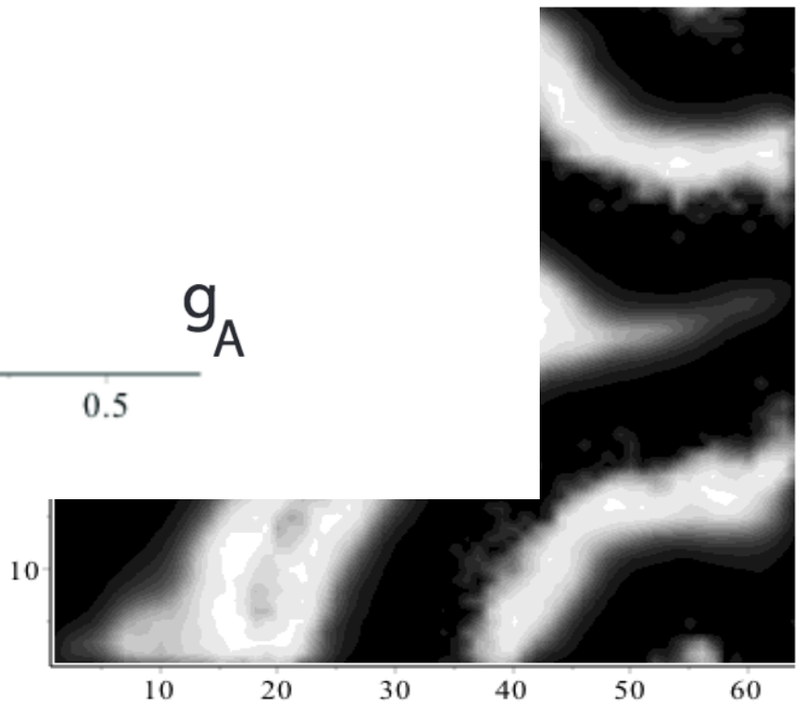




gach=0.126 nS

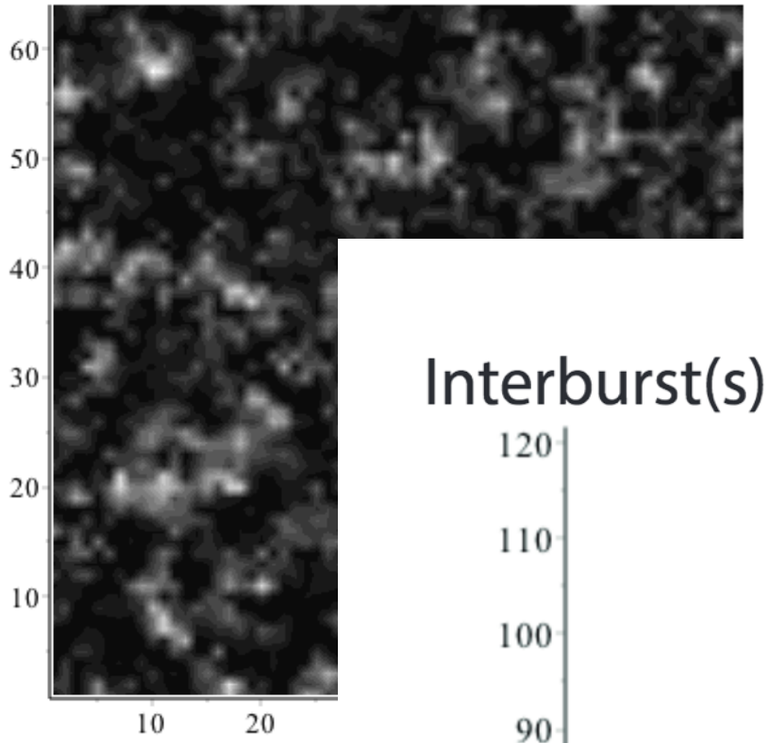


. nS

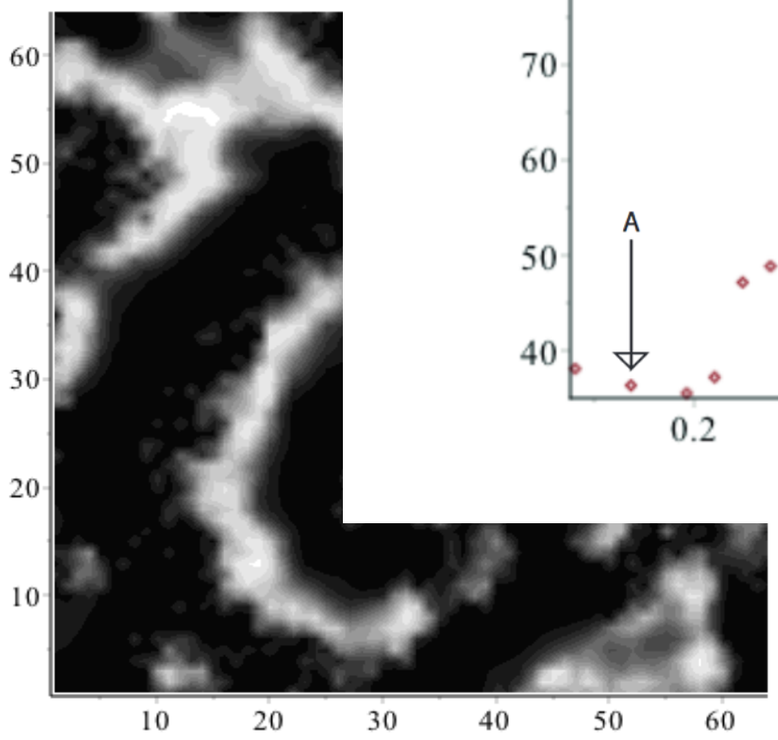


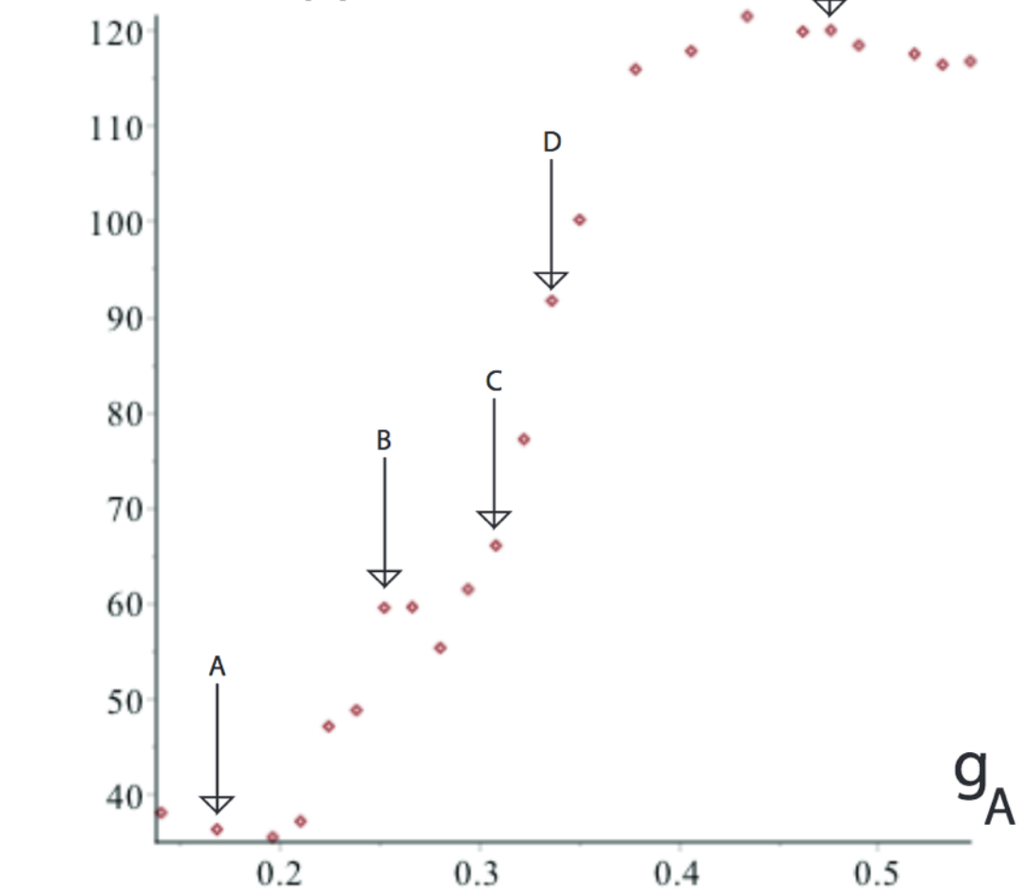
Network of SACs : Simulated Calcium Concentration

gach=0.102 nS

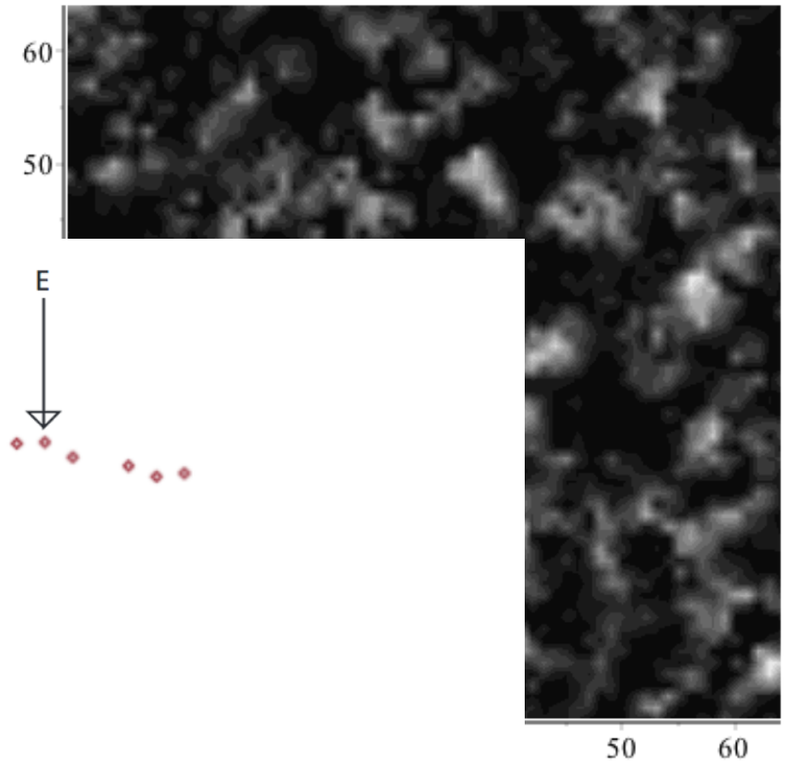


gach=0.

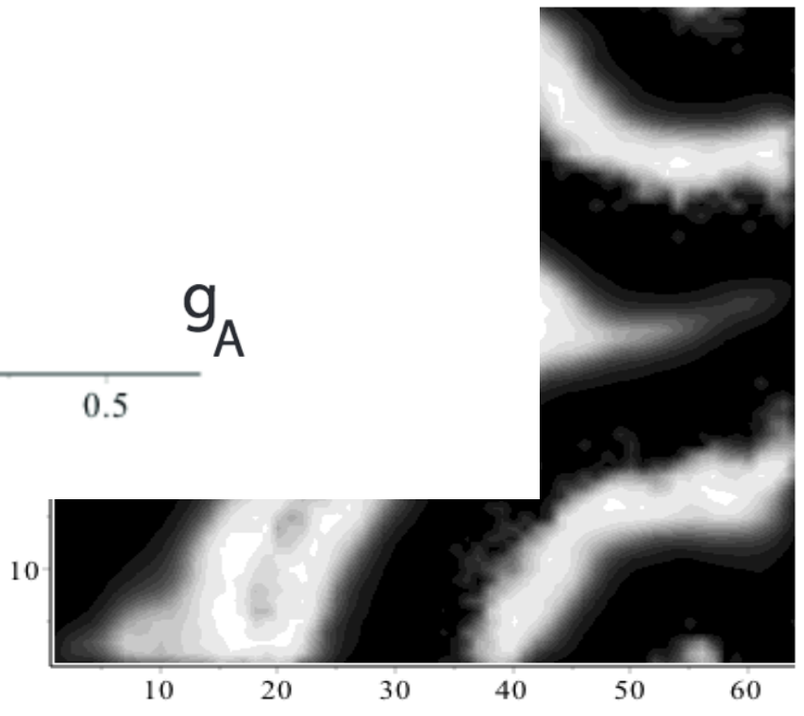


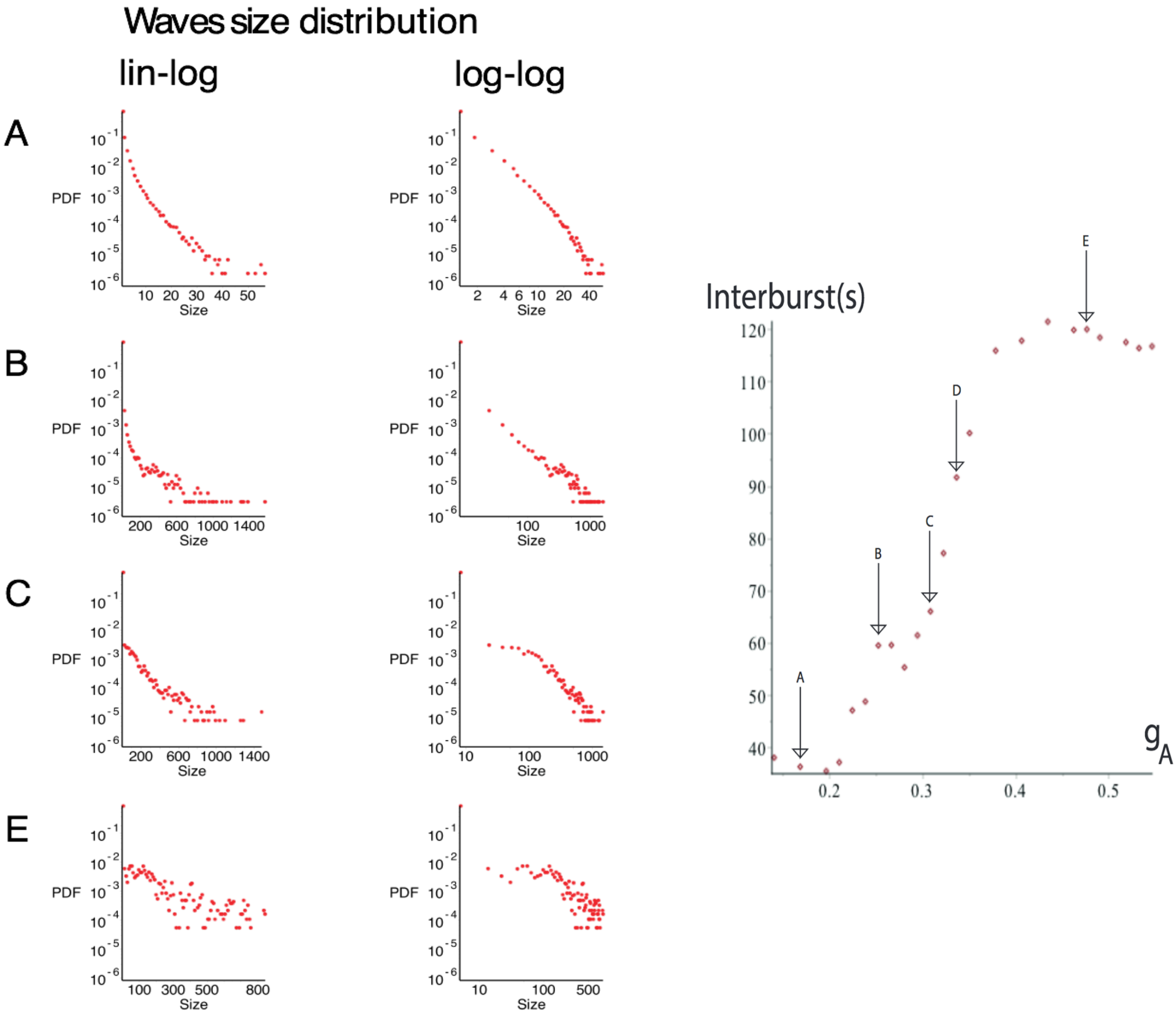


gach=0.126 nS

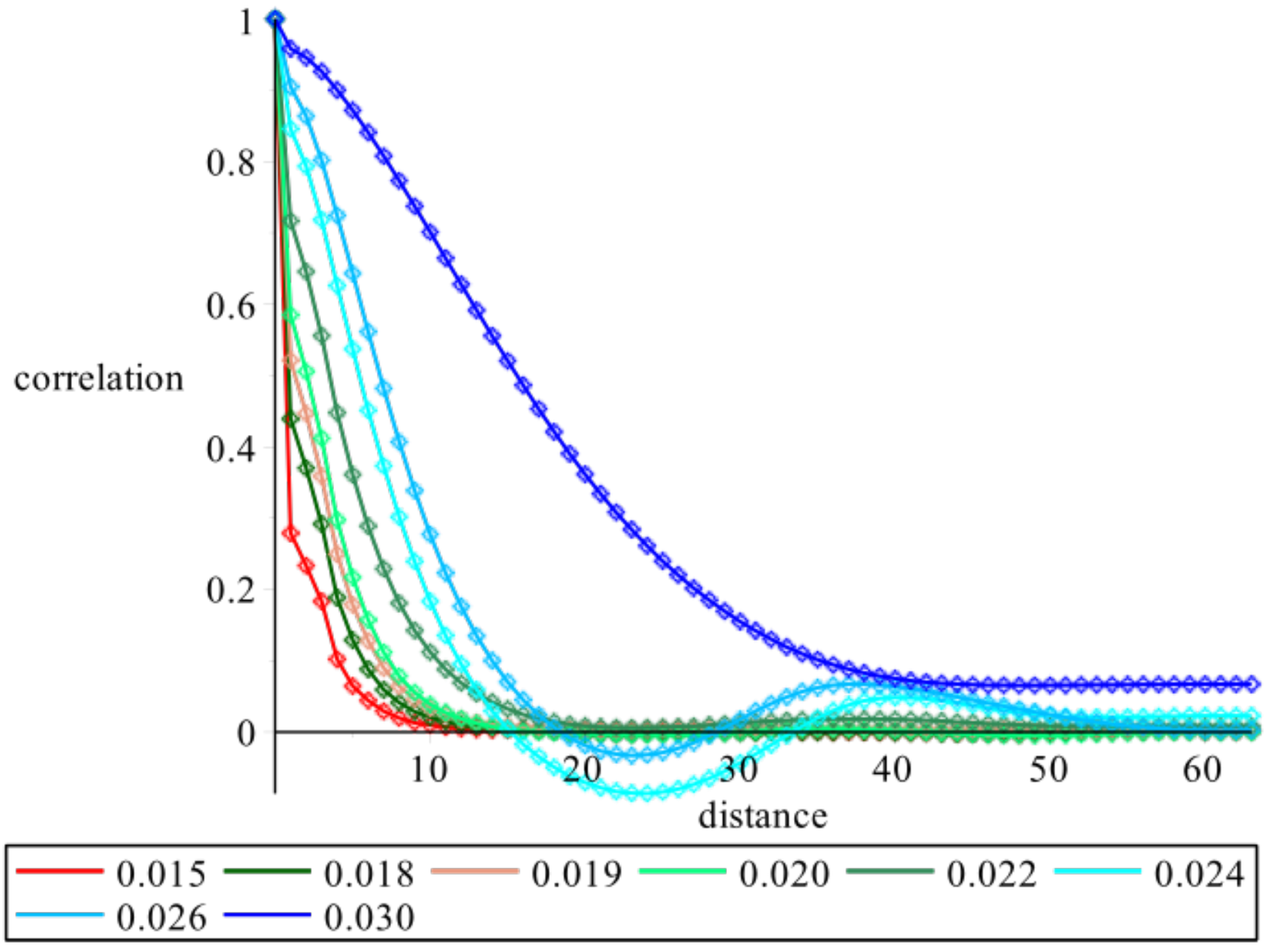


. nS



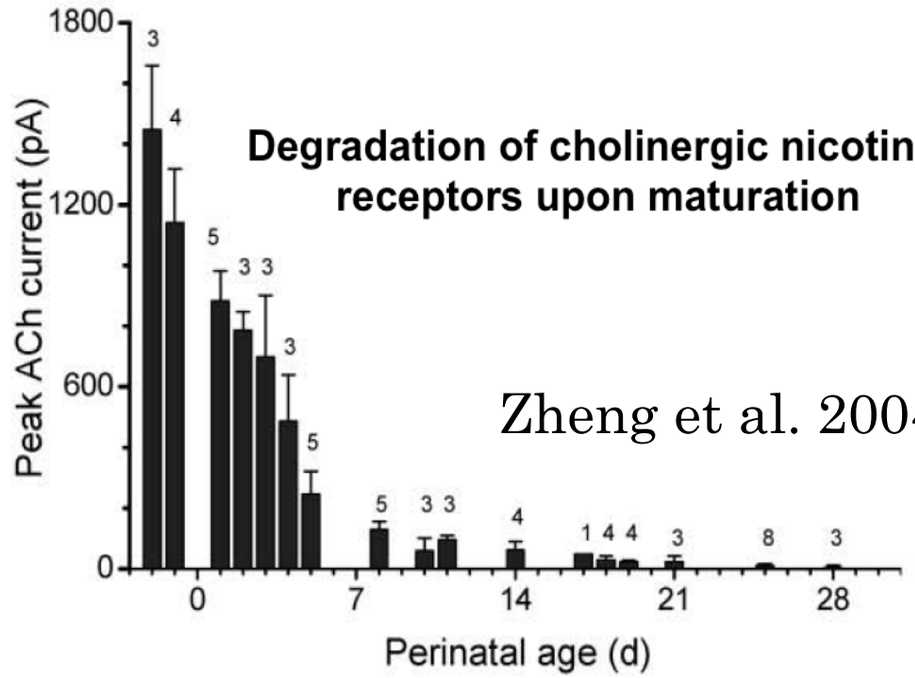

Waves size distribution
lin-log
log-log
A
B
C
E
PDF
Size
Interburst(s)
g_A
A
B
C
D
E

Distance Pairwise Correlations



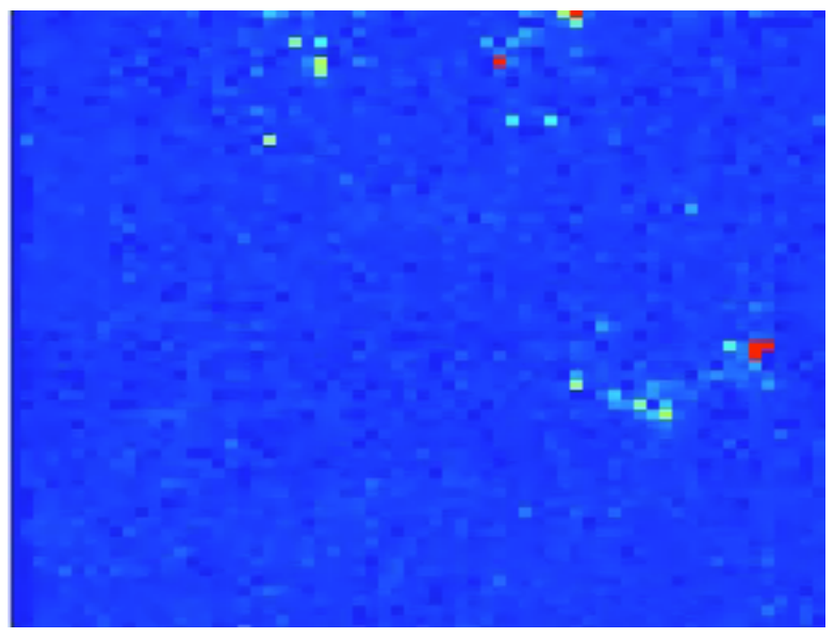
Variability <u>within</u> retinal waves

ii) Development



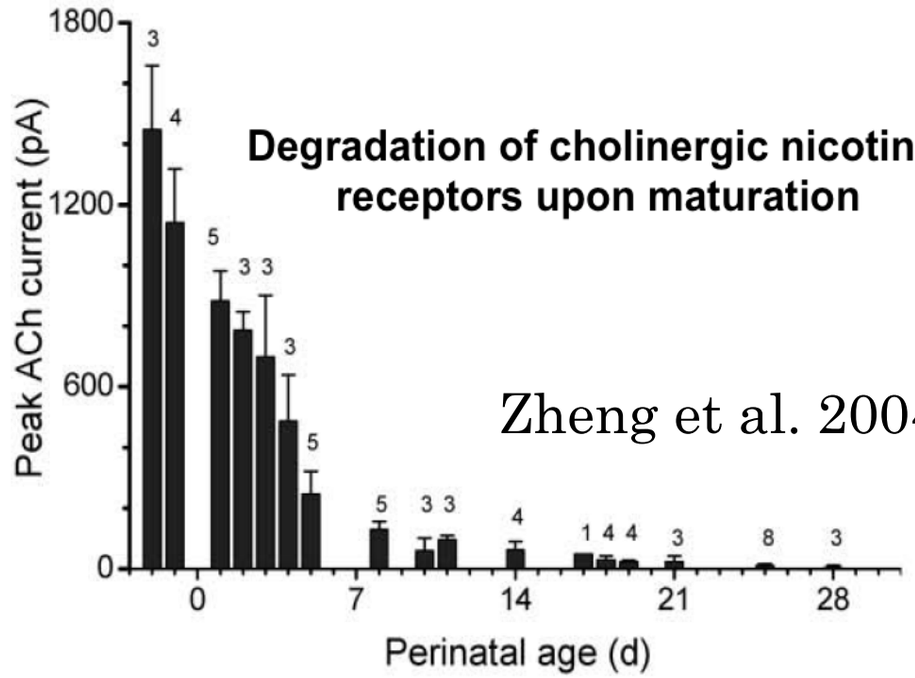
Zheng et al. 2004

iv) Spatial Variability



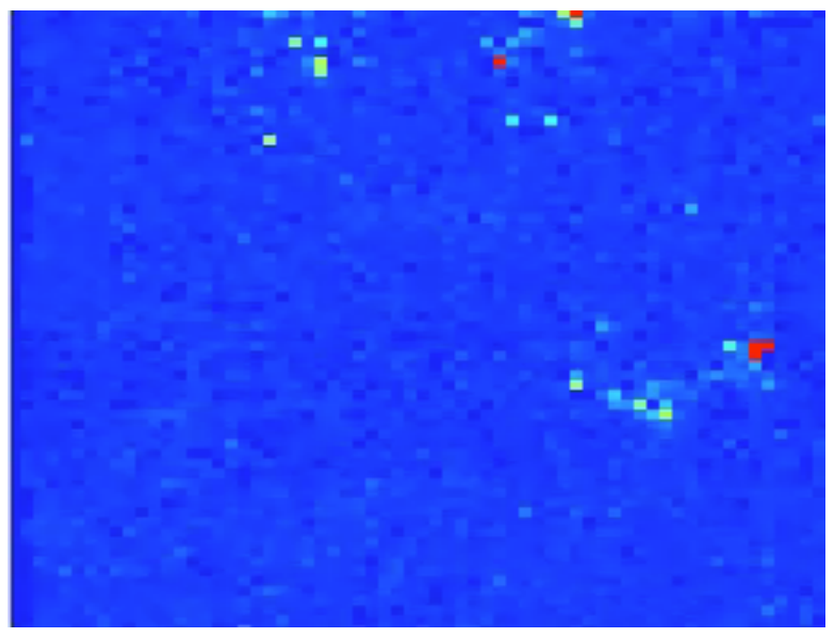
Variability <u>within</u> retinal waves

ii) Development



Zheng et al. 2004

iv) Spatial Variability



Variability within retinal waves

Analytical results

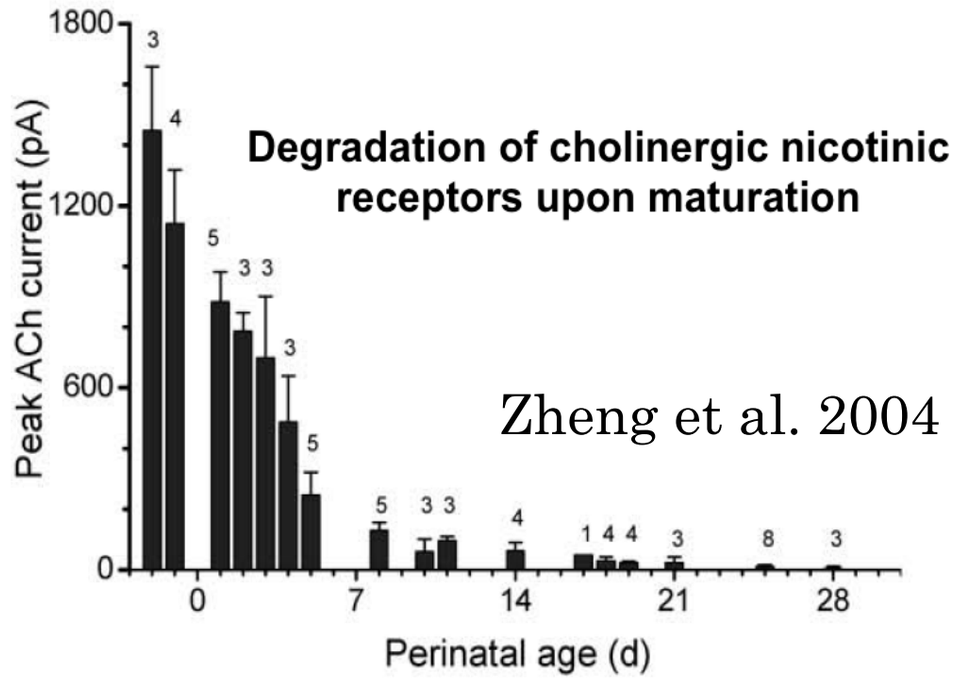
1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.

2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)

3. Waves cannot cross each others => characteristic length, **exponential distribution**.

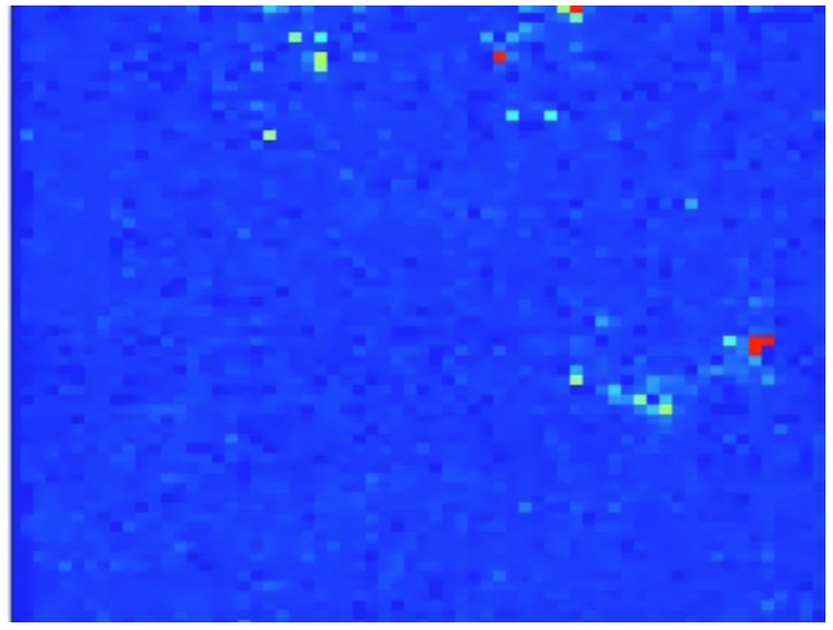
4. There is a critical point where waves are **power law** distributed.

ii) Development



Zheng et al. 2004

iv) Spatial Variability



Variability within retinal waves

Analytical results

1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.

2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)

3. Waves cannot cross each others => characteristic length, **exponential distribution**.

4. There is a critical point where waves are **power law** distributed.

Variability within retinal waves

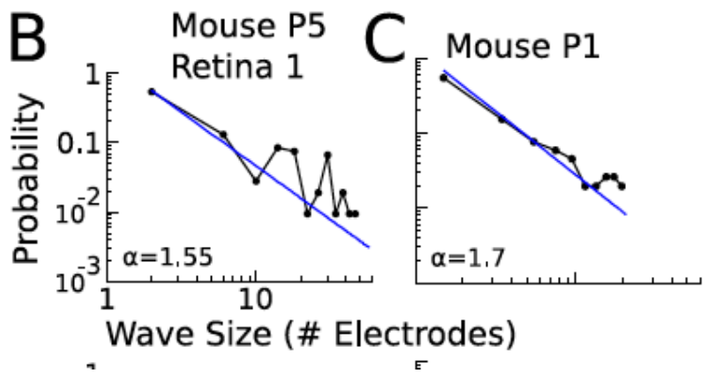
Analytical results

1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.

2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)

3. Waves cannot cross each others => characteristic length, **exponential distribution**.

4. There is a critical point where waves are **power law** distributed.



Hennig et al. 2009

Variability within retinal waves

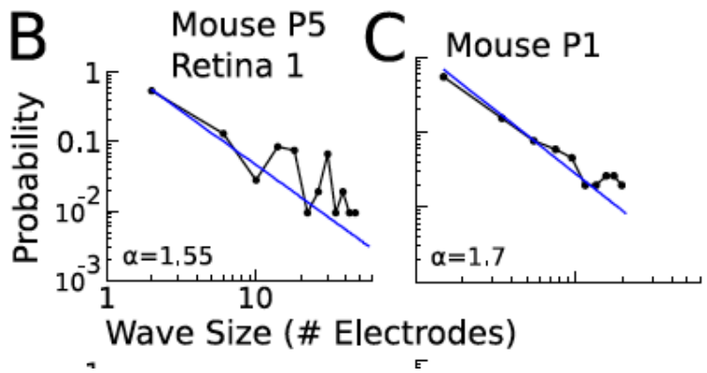
Analytical results

1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.

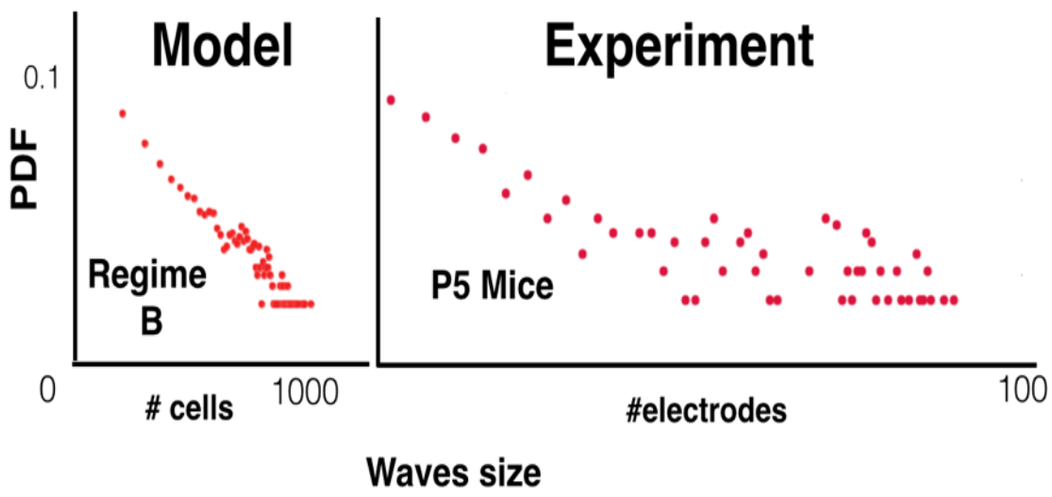
2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)

3. Waves cannot cross each others => characteristic length, **exponential distribution**.

4. There is a critical point where waves are **power law** distributed.



Hennig et al. 2009

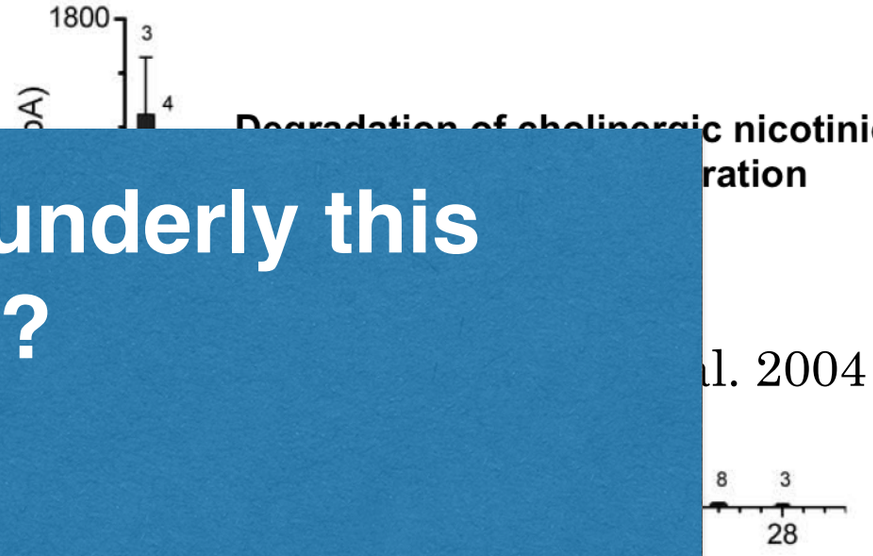


Experimentally varying Ach conductance (Data D. Karvouniari + Institut de la Vision)

Variability within retinal waves

i) Across species

ii) Development



Degradation of cholinergic nicotinic
ration

l. 2004

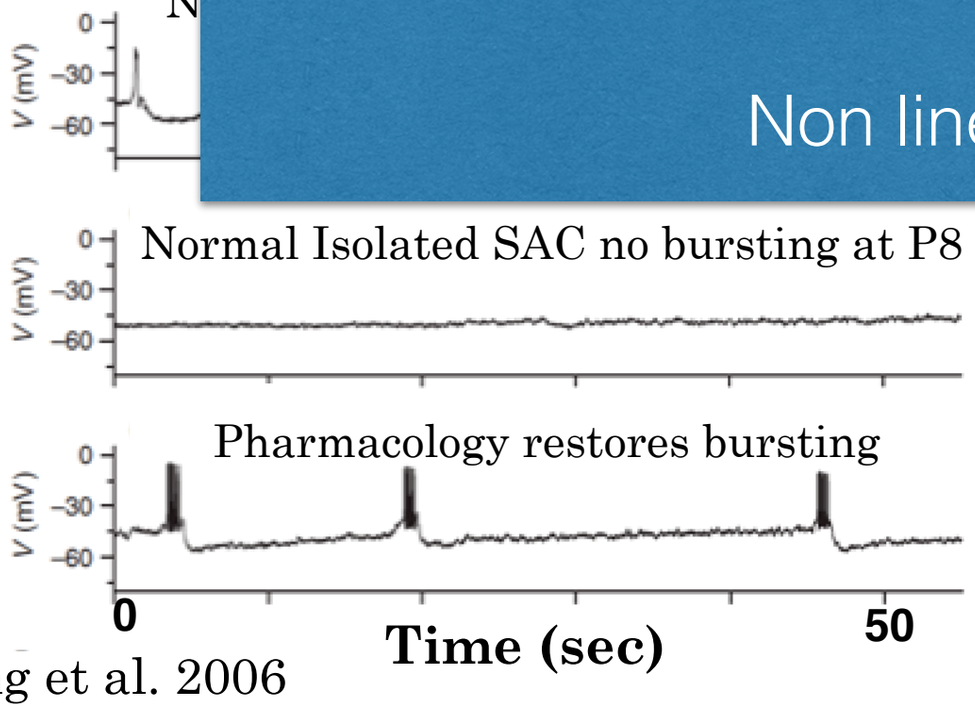
Which mechanisms underly this variability ?

Randomness ?

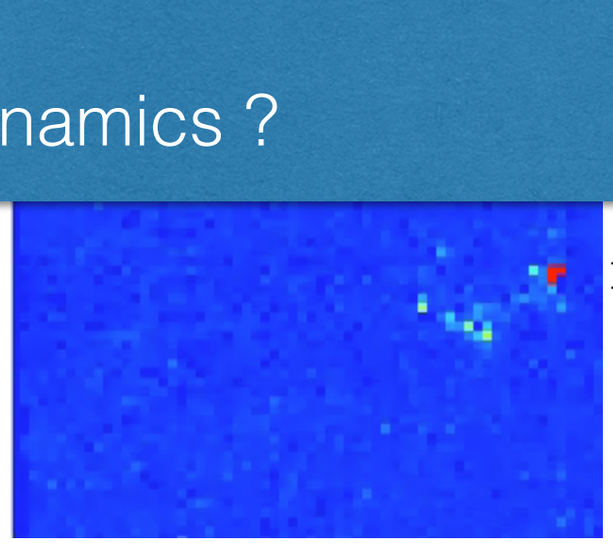
Genetics ?

Non linear dynamics ?

iii) ability



Zheng et al. 2006



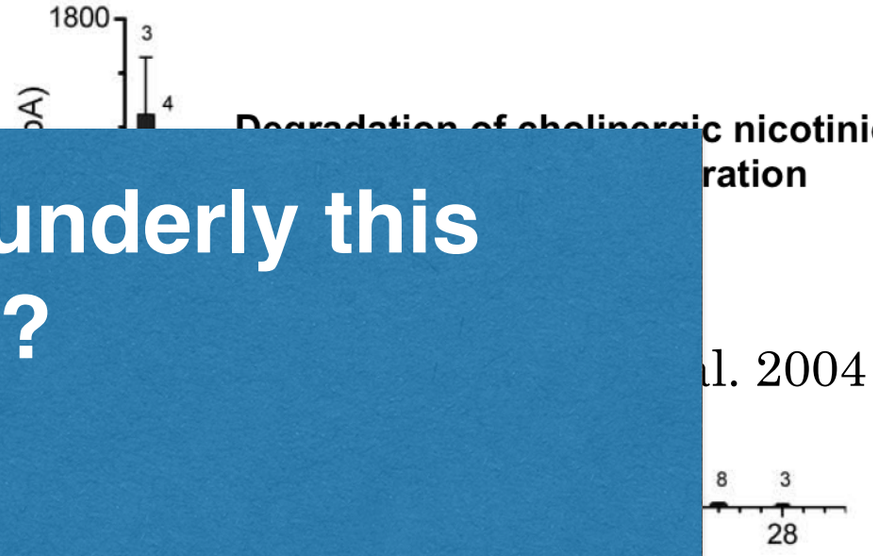
Maccione et al. 2014

have variable
shapes due to a
refractory mechanism
which controls their
borders.

Variability within retinal waves

i) Across species

ii) Development



Degradation of cholinergic nicotinic
ration

l. 2004

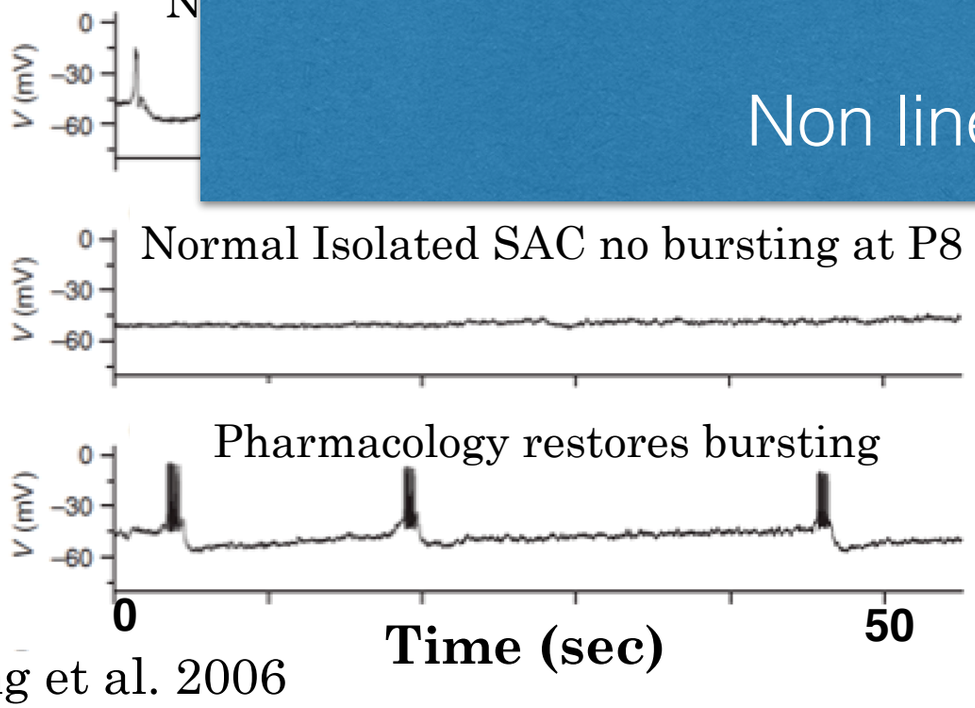
Which mechanisms underly this variability ?

Randomness ?

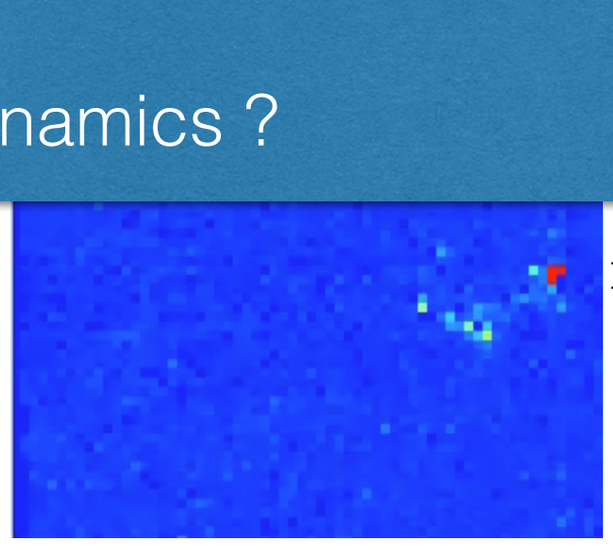
Genetics ?

Non linear dynamics ?

iii) ability



Zheng et al. 2006



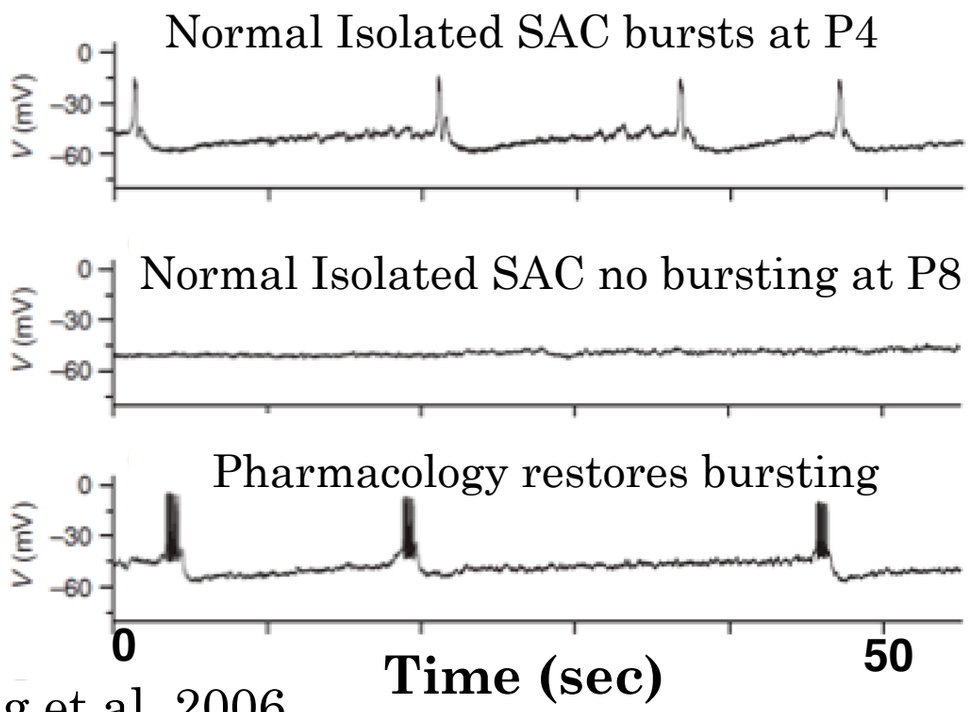
Maccione et al. 2014

have variable
shapes due to a
refractory mechanism
which controls their
borders.

Variability <u>within</u> retinal waves

Variability <u>within</u> retinal waves

iii) Pharmacology



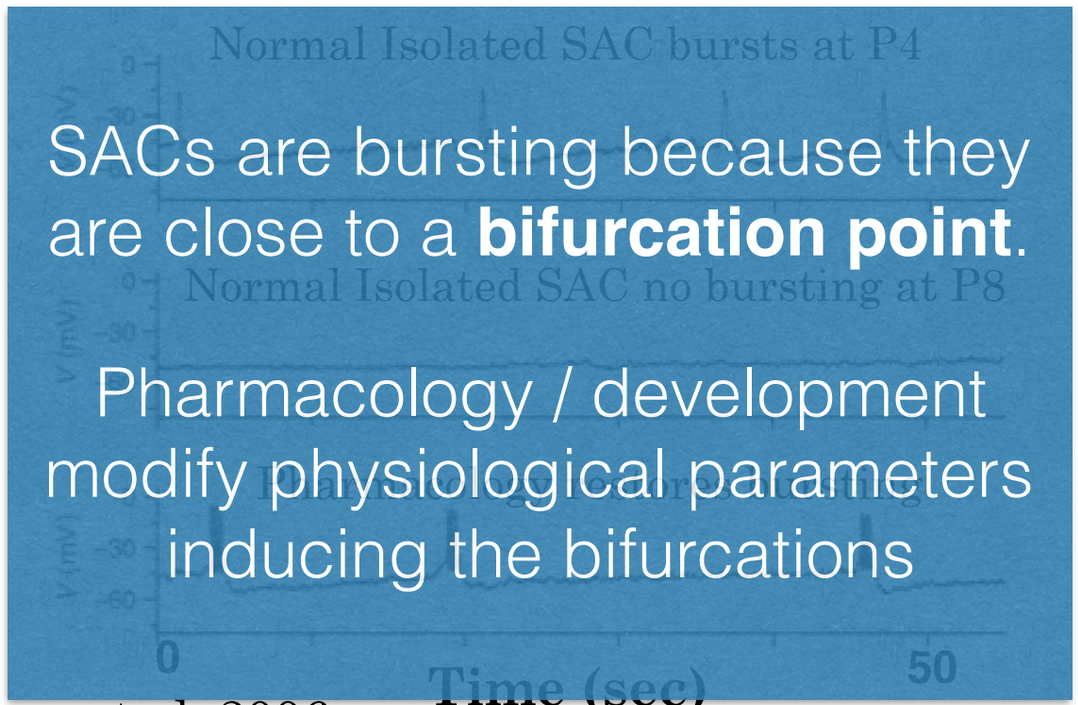
Zheng et al. 2006

Variability <u>within</u> retinal waves

iii) Pharmacology

P4

P8



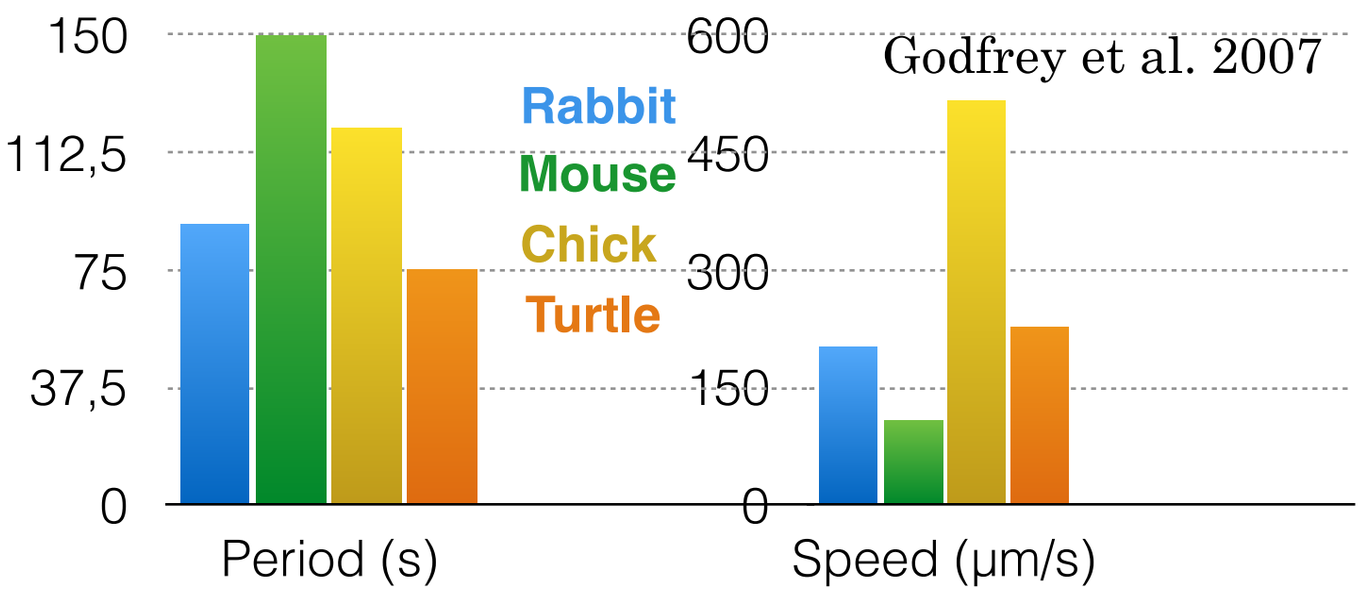
SACs are bursting because they are close to a **bifurcation point**.

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

Variability within retinal waves

i) Across species



iii) Pharmacology

P4

P8

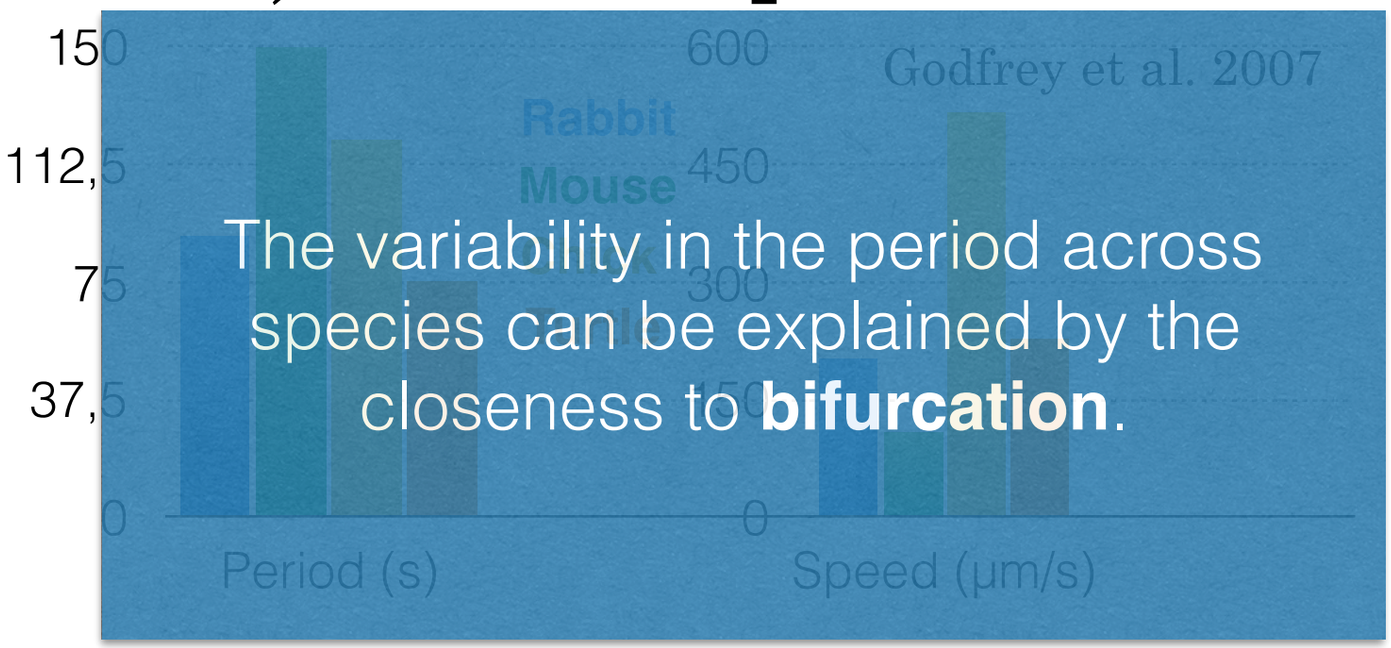
SACs are bursting because they are close to a **bifurcation point**.

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

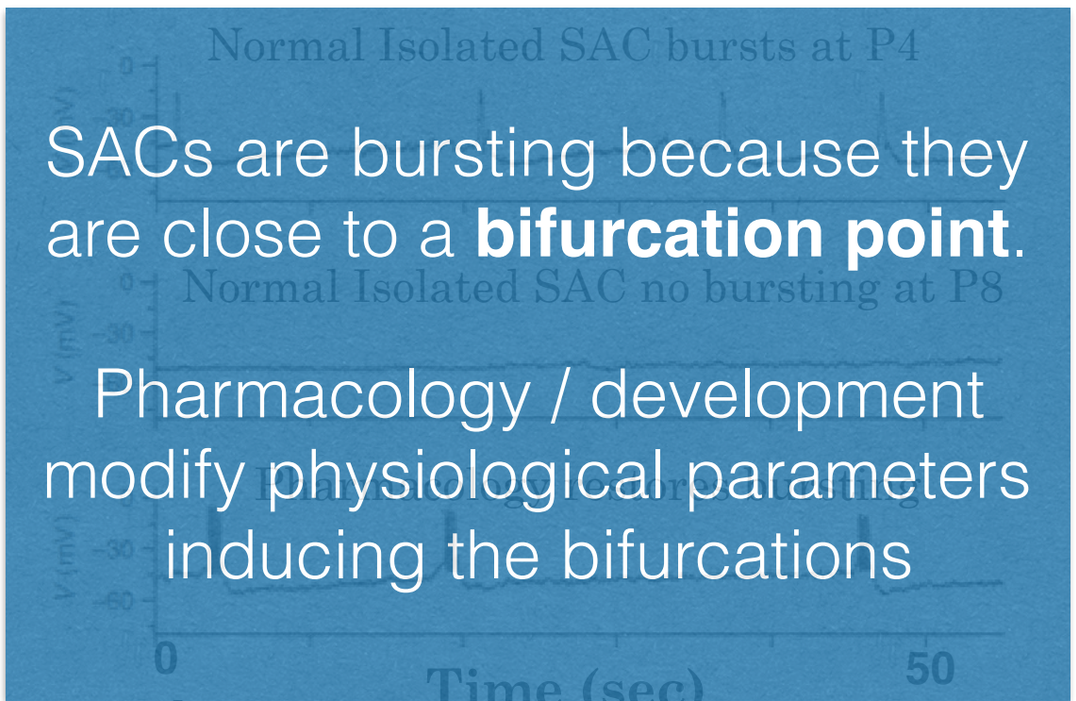
Variability <u>within</u> retinal waves

i) Across species



The variability in the period across species can be explained by the closeness to **bifurcation**.

iii) Pharmacology



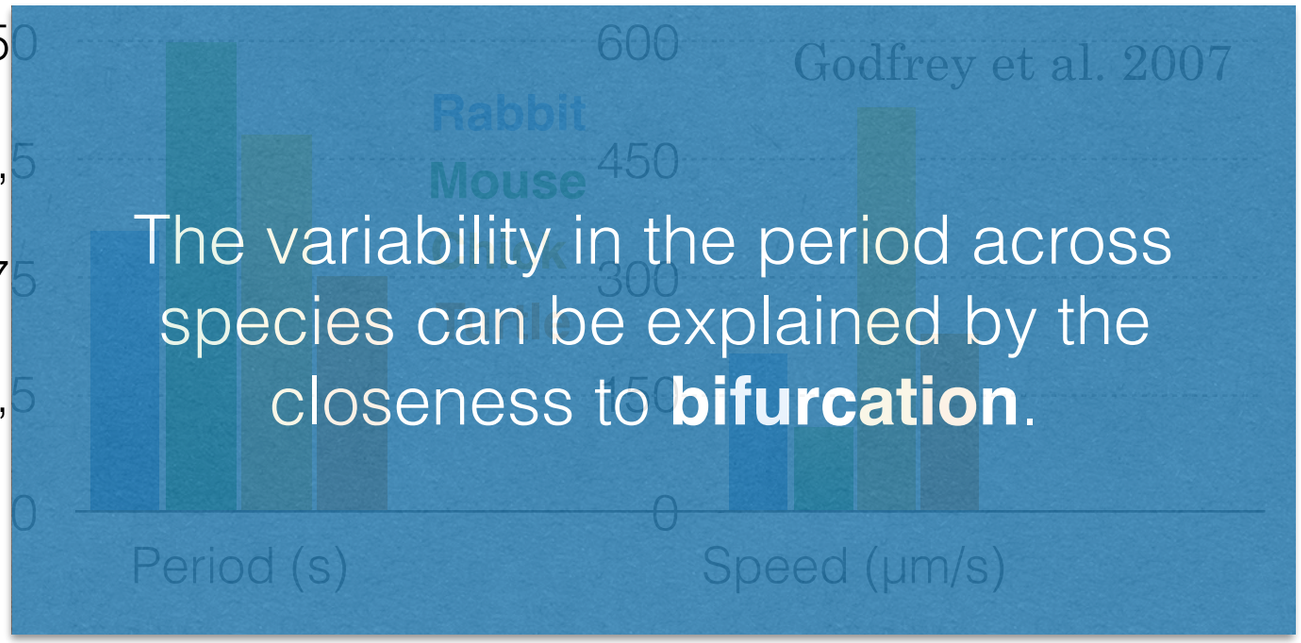
SACs are bursting because they are close to a **bifurcation point**.

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

Variability <u>within</u> retinal waves

i) Across species

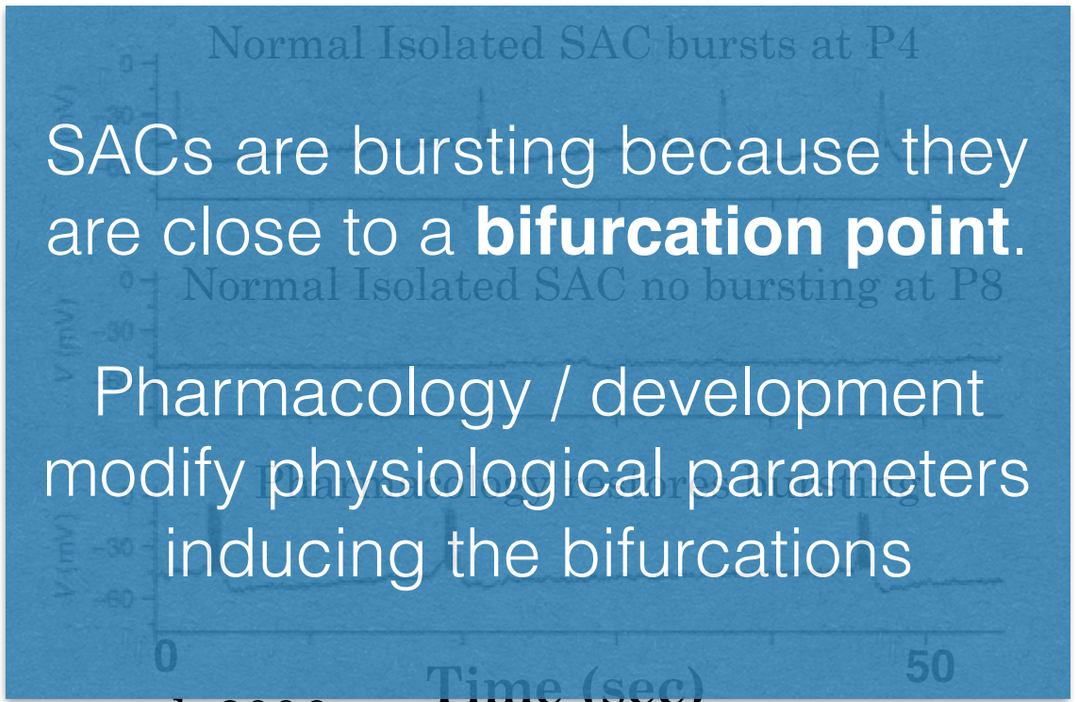


The variability in the period across species can be explained by the closeness to **bifurcation**.

iii) Pharmacology

P4

P8

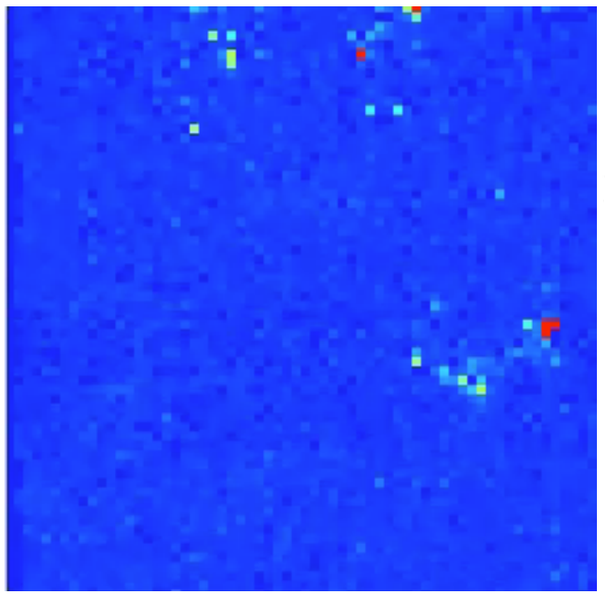


SACs are bursting because they are close to a **bifurcation point**.

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

iv) Spatial Variability

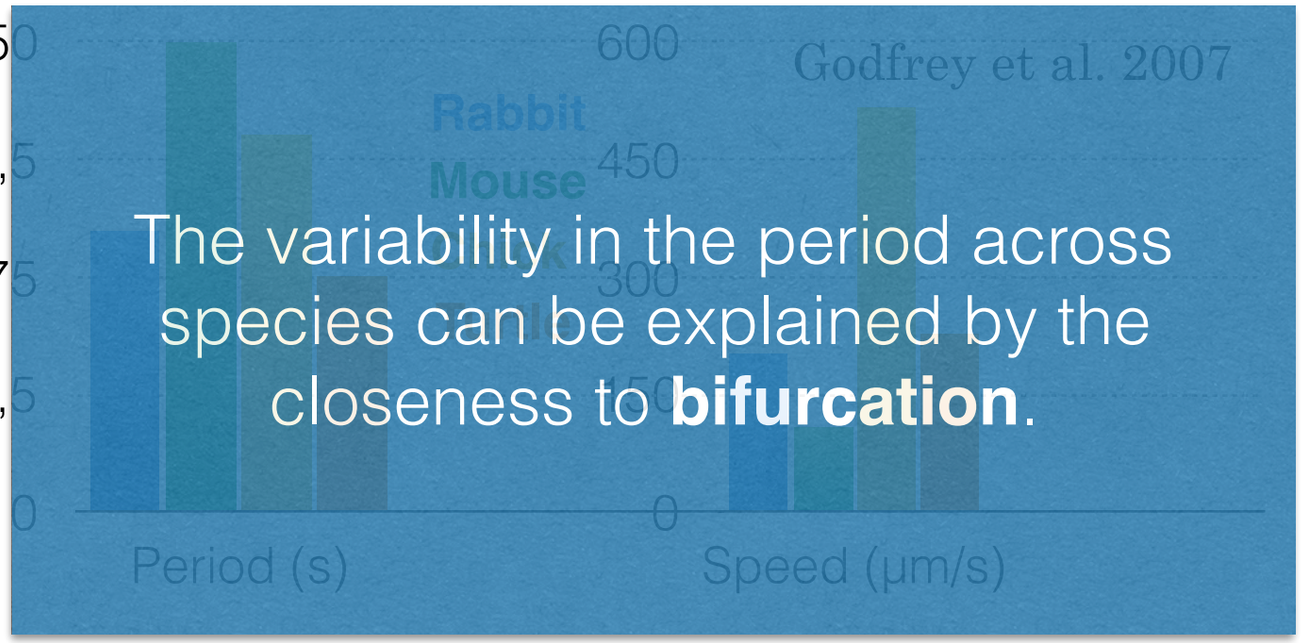


Maccione et al. 2014

Waves have variable shapes due to a refractory mechanism which controls their borders. It is called sAHP (**s**low **A**fter**H**yper **P**olarization) for stage II.

Variability <u>within</u> retinal waves

i) Across species

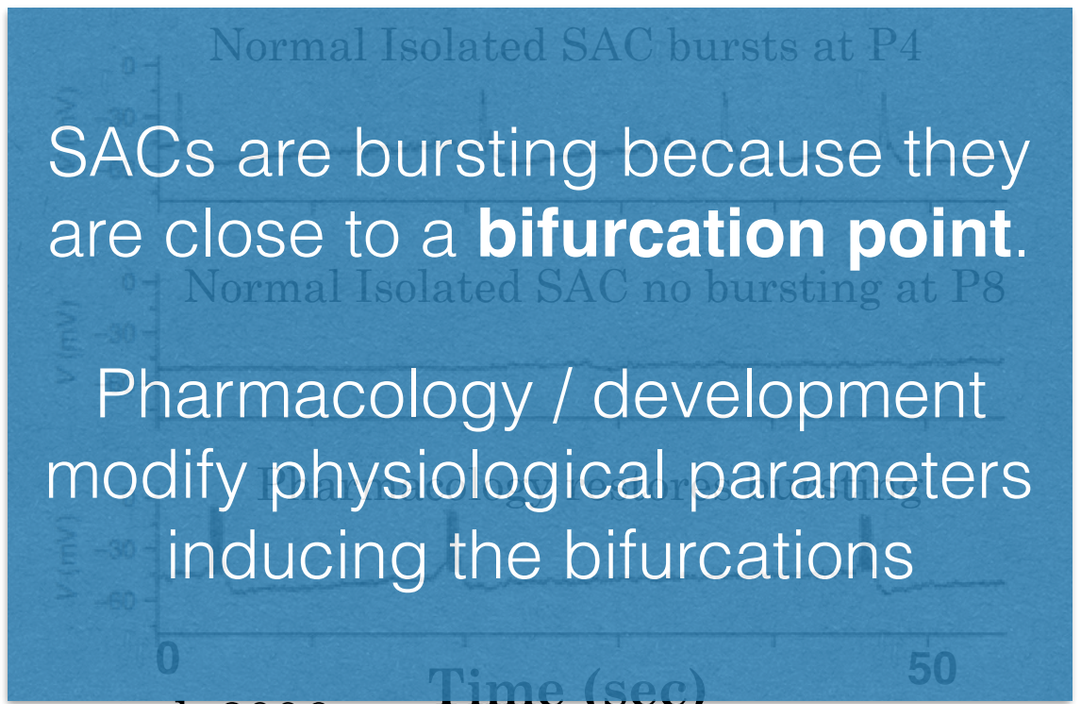


The variability in the period across species can be explained by the closeness to **bifurcation**.

iii) Pharmacology

P4

P8

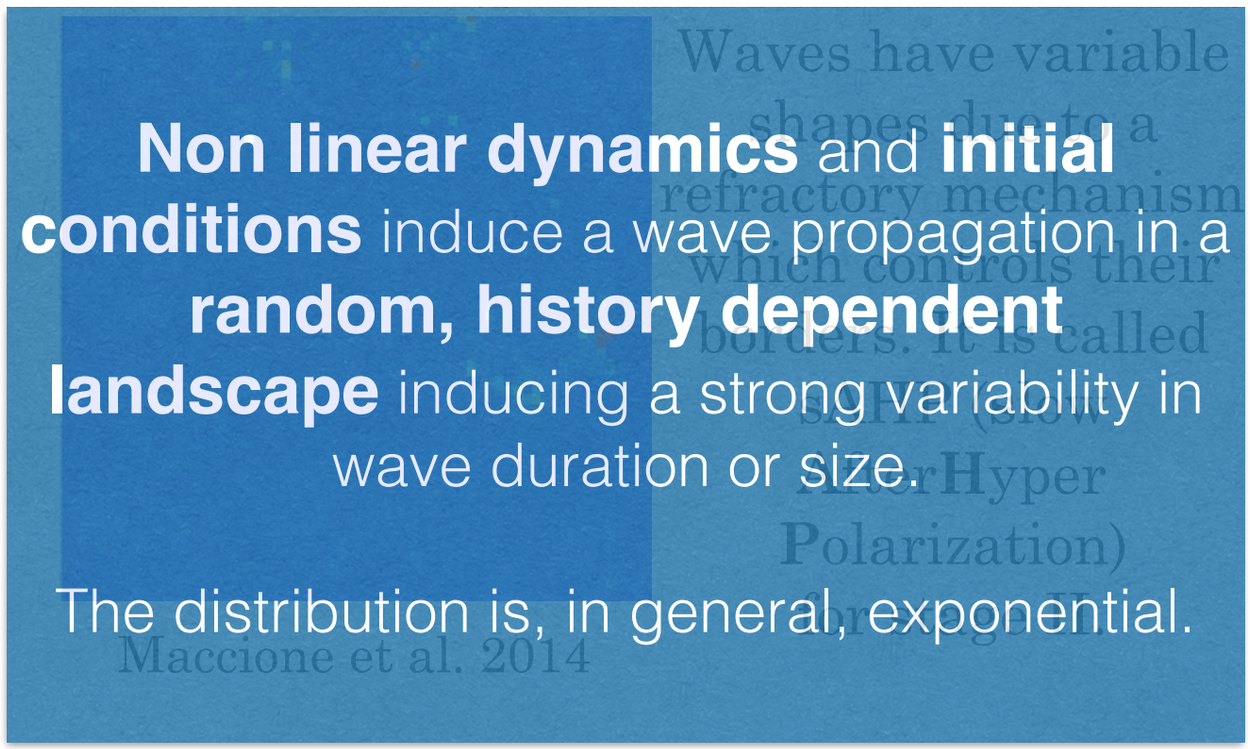


SACs are bursting because they are close to a **bifurcation point**.

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

iv) Spatial Variability

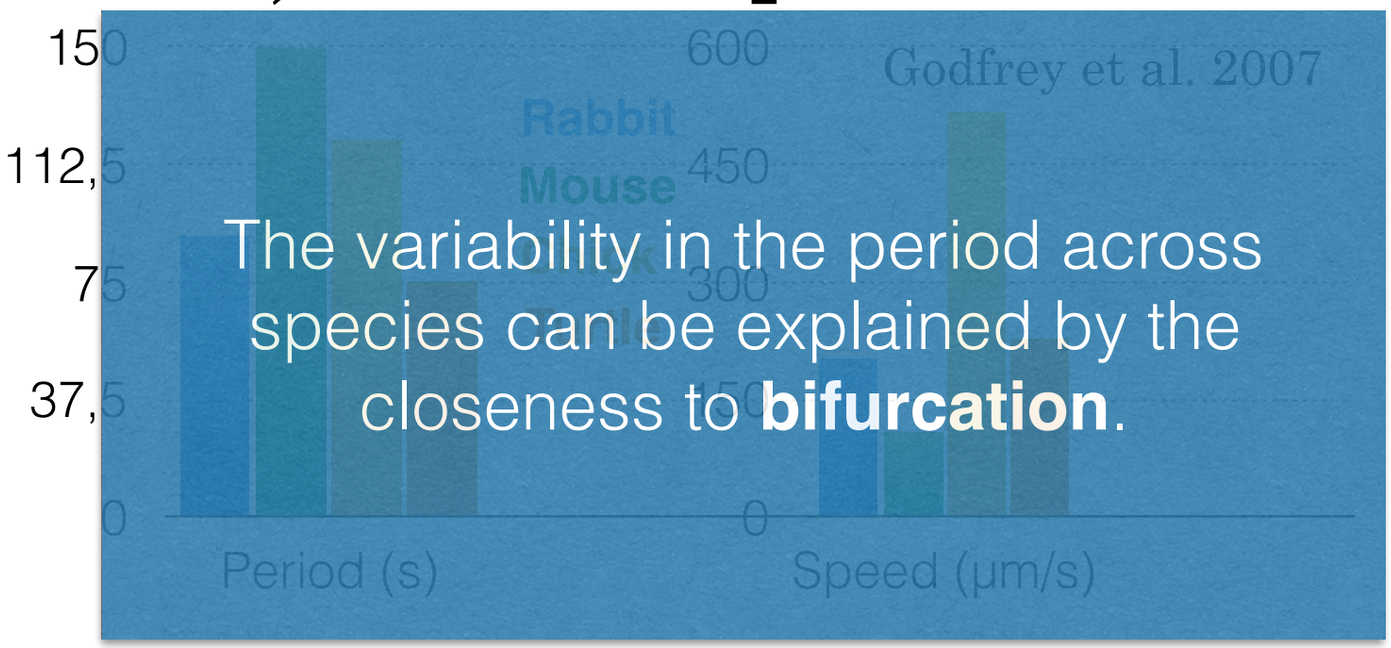


Non linear dynamics and **initial conditions** induce a wave propagation in a **random, history dependent landscape** inducing a strong variability in wave duration or size.

The distribution is, in general, exponential.

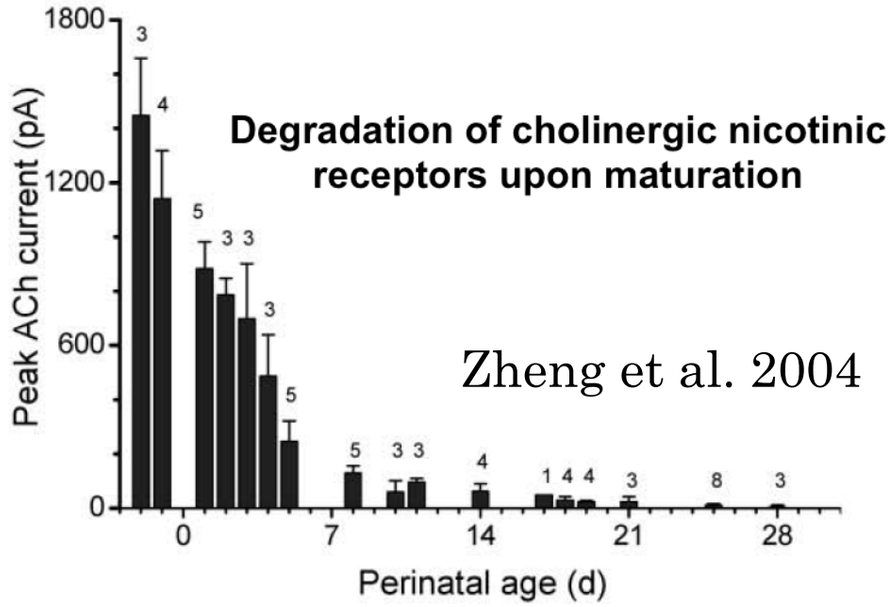
Variability within retinal waves

i) Across species

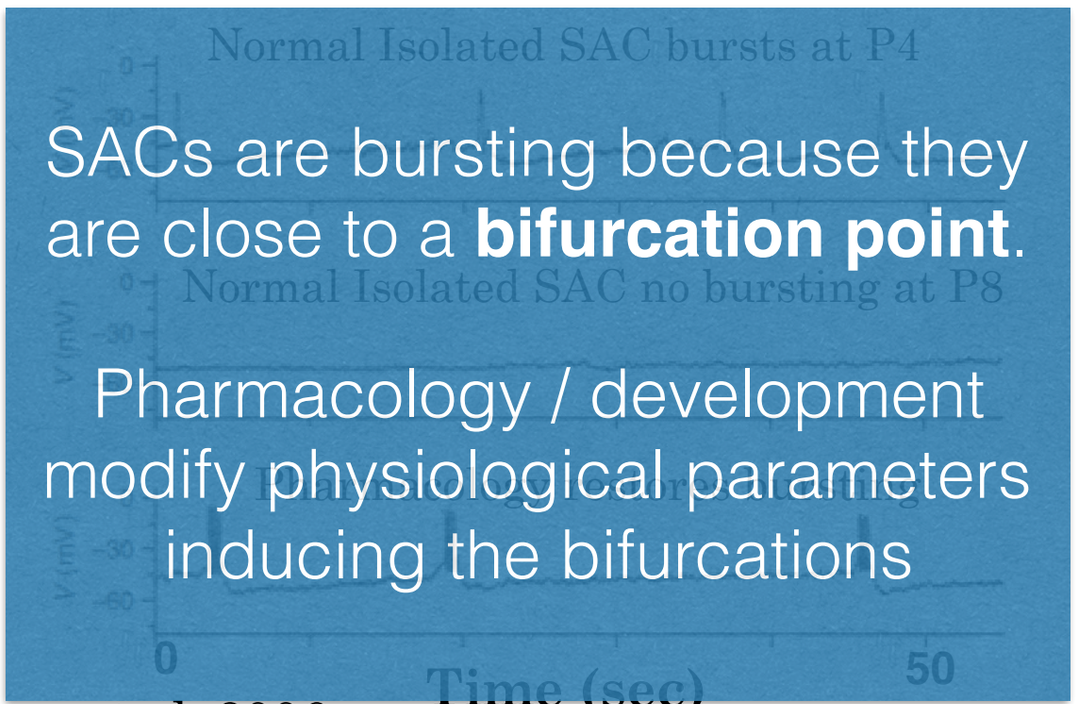


The variability in the period across species can be explained by the closeness to **bifurcation**.

ii) Development



iii) Pharmacology



SACs are bursting because they are close to a **bifurcation point**.

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

iv) Spatial Variability

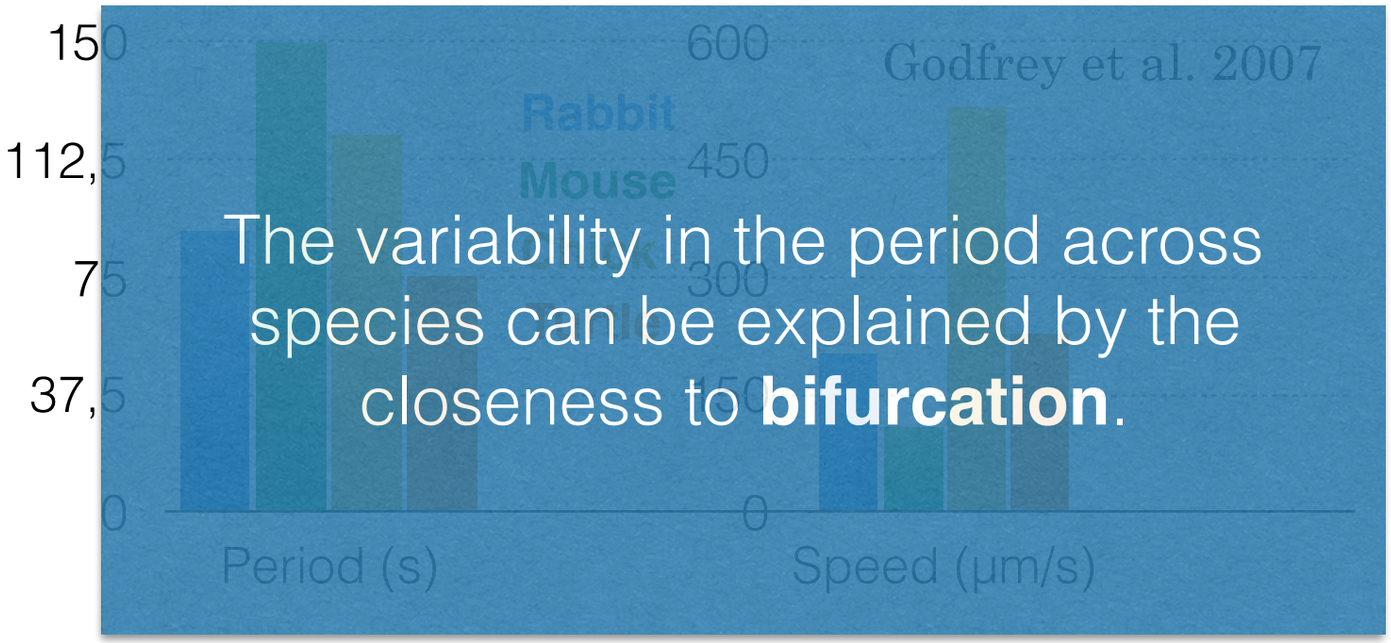
Non linear dynamics and **initial conditions** induce a wave propagation in a **random, history dependent landscape** inducing a strong variability in wave duration or size.

The distribution is, in general, exponential.

Maccione et al. 2014

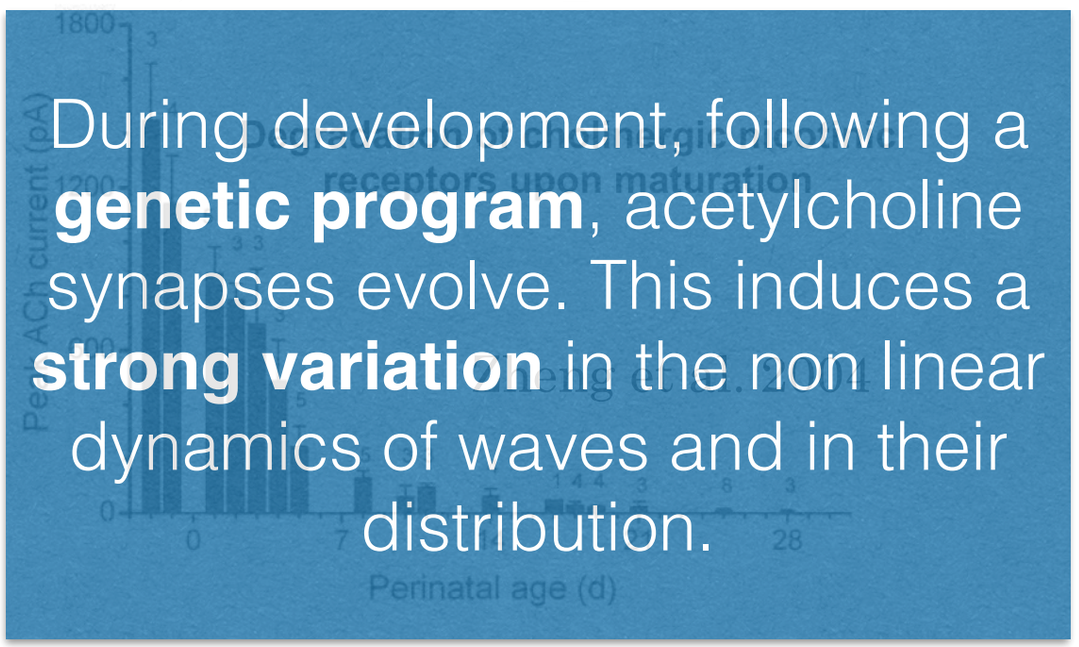
Variability within retinal waves

i) Across species



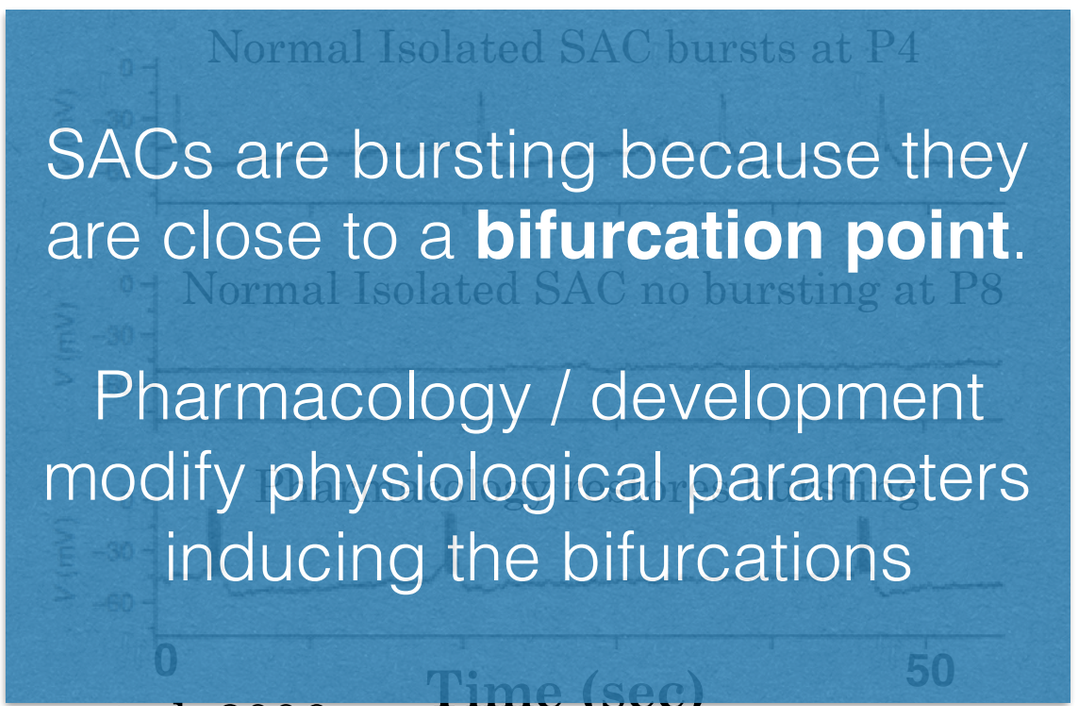
The variability in the period across species can be explained by the closeness to **bifurcation**.

ii) Development



During development, following a **genetic program**, acetylcholine synapses evolve. This induces a **strong variation** in the non linear dynamics of waves and in their distribution.

iii) Pharmacology

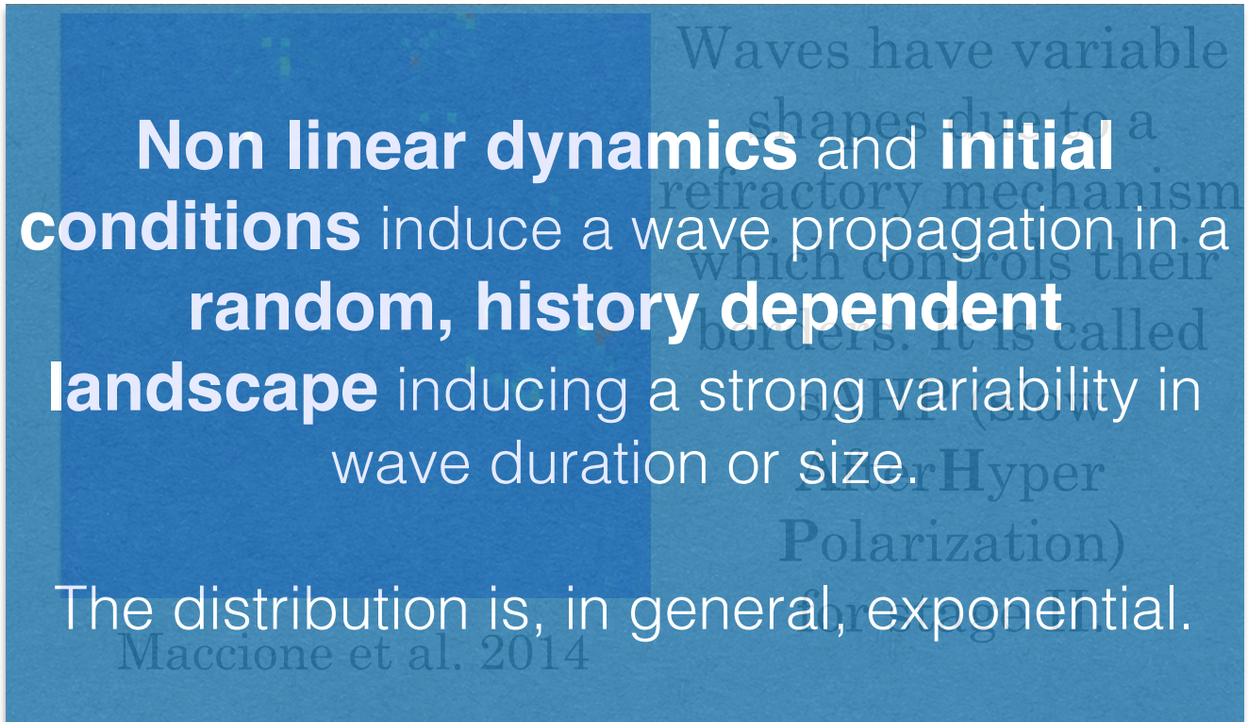


SACs are bursting because they are close to a **bifurcation point**.

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

iv) Spatial Variability



Non linear dynamics and **initial conditions** induce a wave propagation in a **random, history dependent landscape** inducing a strong variability in wave duration or size.

The distribution is, in general, exponential.

Variability within retinal waves

i) Across species

ii) Development

Is there a benefit for the visual system, at this stage of development, to generate power law distributed waves ?

iii) Which mechanism could enable this fine tuning ? Homeostasis ?

P4

P8

Pharmacology / development modify physiological parameters inducing the bifurcations

Zheng et al. 2006

wave duration or size.

The distribution is, in general, exponential.

Maccione et al. 2014

Thanks